

Thank you kindly for your letters in response to the AHRQ Draft systematic evidence review on Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. And thank you for sharing your individual stories with our team. The devastating effects that this condition has had on your lives and those of other patients are better appreciated by allowing us the opportunity to see into your world for even a short time. Although we cannot experience the condition as a patient would, we included patients and experts as members of our technical expert panel, and strove to attend to their areas of concern and guidance as we prepared our report. It is however, our responsibility as independent investigators to strictly report on evidence that is currently available using a pre-defined and structured systematic method.

In the Disposition of Comments, we have redacted names of those who identified themselves for purposes of maintaining confidentiality and privacy. Where possible, we have also consolidated comments that were almost identical. However all the correspondences received are included verbatim in the appendix following the disposition tables.

Please understand that we do hear your disappointment and frustration with the current state of the research. However, through efforts such as this, researchers are truly striving to better understand ME/CFS with the universal goal of improving the quality of life and experience of patients.

Respectfully,

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Evidence Report/Technology Assessment Disposition of Comments Report

Research Review Title: *Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome*

Draft review available for public comment from September 23, 2014, to October 20, 2014.

Research review citation: Smith MEB, Nelson HD, Haney E, Pappas M, Daeges M, Wasson N, McDonagh M. Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Evidence Report/Technology Assessment No. 219. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-I.) AHRQ Publication No. 15-E001-EF. Rockville, MD: Agency for Healthcare Research and Quality; December 2014. www.effectivehealthcare.ahrq.gov/reports/final/cfm.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each research review is posted to the EHC Program Web site in draft form for public comment for a 4-week period. Comments can be submitted via the EHC Program Web site, mail or email. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft comparative effectiveness research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Executive Summary	In the executive summary it states on page 9: "The most recent international consensus report advocates moving away from the term CFS in favor of ME to better reflect an underlying pathophysiology involving widespread inflammation and neuropathology, and to embrace the two terms as synonymous." The ME term (indicates brain and spinal cord inflammation) does not better reflect underlying pathology because the underlying pathology has not been identified. We have disparate evidence from a broad array of specialties (immunology, euroendocrinology, genomics, metabolic function). Actually the evidence for brain inflammation is minimal if not non-existent.	Thank you for your comment. In Carruthers et al, 2011, the authors write: "In view of more recent research and clinical experience that strongly point to widespread inflammation and multisystemic neuropathology, it is more appropriate and correct to use the term 'myalgic encephalomyelitis' (ME) because it indicates an underlying pathophysiology." We appreciate that an underlying etiology has not been conclusive and have changed the wording to the following: "The most recent international consensus report advocates moving away from the term CFS in favor of ME."
PD White, T Chalder, R Moss-Morris, M Sharpe, AJ Wearden	Executive Summary	The abstract states: "Although adverse effects were not well reported across trials, GET compared with CBT or control groups was associated with a higher number of reported adverse events and withdrawal rates in several trials", and in the conclusions – "GET appears to be associated with harms in some patients..." The first statement seems to imply that adverse effects of a treatment are the same as adverse events that occur when receiving a treatment, when this is not the case. Adverse "effects" are caused by a treatment, which is why they are more commonly called adverse "reactions", whereas adverse events are not necessarily related to a treatment and may be more related to the natural course of the illness or a comorbid illness. We note that the current draft confuses adverse events with harms due to treatment throughout the document.	Thank you for this clarification. We have changed our wording throughout the report for clarity with definitions as applicable.
PD White, T Chalder, R Moss-Morris, M Sharpe, AJ Wearden	Executive Summary	ES-28 "The harms associated with exercise were generally more implied than specifically stated in the exercise trials.67-70 In the combination trials, the greatest number of harms were in the GET arm of one trial, 69 lowest adherence was in the exercise arm in another trial, 68 and several trials had greatest withdrawal due to adverse events in the exercise arms.67,70" We suggest that there are a number of errors in these statements, which we detail below.	Thank you. We have expanded our discussion of the adverse outcomes and harms for better clarity in the report.

Commentator & Affiliation	Section	Comment	Response
PD White, T Chalder, R Moss-Morris, M Sharpe, AJ Wearden	Executive Summary	ES-12 and Page 21 "... patients receiving GET reported more adverse effects compared with CBT, adaptive pacing, or usual care in one good-quality trial.." This statement referring to the PACE trial (www.pacetrail.org), of which some of us we were the principal investigators, is a misinterpretation of the trial results, and does not take into account statistical significance. The safety data from this trial were given in table 4 of White et al, 2011, which shows the results of six different adverse outcomes across the four arms of the trial. Most importantly there were very few serious adverse reactions to treatment (i.e. adverse treatment effects), with no statistical difference across treatment arms. Although there were more serious adverse events (SAEs) in GET compared to CBT and specialist medical care alone (SMC), there was a similar number in the adaptive pacing therapy (APT) arm, and, of course, SAEs were judged to be independent of treatment by independent scrutineers. Therefore it would be inaccurate to interpret SAEs as evidence of harm relating to treatment. Similarly there were no statistically significant differences in the proportions suffering from serious deterioration. In particular there were no differences in withdrawals from treatment due to worsening across treatment arms (this result needs to be incorporated into the table on ES-23 and ES-22).	Thank you for your comments. We have reviewed the harms reporting in the PACE trial and edited our discussion to better reflect the harms reported. We have also expanded our discussion of the limitations of the trial, including the way that adverse events were reported and the definitions of serious vs. non-serious adverse events vs. serious adverse reactions, and the subjective interpretation of these by investigators.
PD White, T Chalder, R Moss-Morris, M Sharpe, AJ Wearden	Executive Summary	ES-12 "...and there were more withdrawals in the GET group in several trials." This is not the case. There have been 6 RCTs of GET for CFS published (Fulcher, Powell, Wearden, Moss-Morris, Wallman, White), although there are published trials of other exercise interventions. The proportions withdrawing from GET versus the control arm were similar in all but one trial (Wearden et al, 1998). The proportions of participants withdrawing from GET in the largest (PACE) trial were the smallest (6%) compared to all other treatment arms (7, 9, and 11%), although differences were not significant (White et al, 2011; table 2). Wearden's (1998) trial intervention was designed as a fitness training intervention rather than graded exercise therapy. The intervention had higher starting levels of exercise intensity than the other trials, and exercise progression was based on change in heart rate, which probably explains the higher drop-out rates (Wearden et al, 1998).	Thank you for your comments. We have reviewed the withdrawal rates of the trials where this data is available and reported them accordingly.

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PD White, T Chalder, R Moss-Morris, M Sharpe, AJ Wearden	Executive Summary	ES-28 “Several previous studies have found worsening effects with exercise and a survey sponsored by the ME Association found that patients believed that GET made more people worse compared with other treatments. ^{71,72} ” The problem with generalising from surveys of patient organisations are two-fold: 1) We do not know what the survey members’ diagnoses were, and we are aware of one study showing high rates of non-CFS diagnoses in such a patient organisation. Brimmer and colleagues (2013) found that 59% of 49 US patient support group members had an exclusionary condition, and only 35% met criteria for CFS. 2) We do not know if they really did receive graded exercise therapy; one qualitative study of such a survey found significant variation in content and delivery of treatment received (Gladwell et al, 2014). Since the randomised controlled trials do not generally suggest that harm follows GET, we suggest that caution is necessary before generalising from such surveys.	Thank you for your comments. We agree and have edited the discussion accordingly.
Peer Reviewer #5	Executive Summary	I am surprised to see on page ES-29 the statement that “experts have identified critical features of the condition including PEM [post-exertional malaise], however, current methods of testing, comparing, and monitoring this symptom are lacking. “ This is not true, as can be seen in non-reviewed studies http://www.ncbi.nlm.nih.gov/pubmed/20937116 , http://www.ncbi.nlm.nih.gov/pubmed/23813081 . Both objective CPETs, actometers, and survey forms can monitor this symptom.	Thank you for your comments. We have edited this section to indicate that the diagnosis and treatment of specific symptoms of ME/CFS were beyond the scope of this review.
Public Reviewer # 1	Executive Summary	Structured Abstract is misleading. It would be helpful if it could be rewritten so that it reflects what is in the actual document. Some specific suggestions are included below. 1. Leaves the reader with a more positive impression about the evidence and conclusions than is evident when the report is actually read ... 2. It does not accurately reflect the uncertainty that characterizes and permeates the findings of the review. It reports on some of the findings but it does not include some very important limitations. The effect of this omission gives a distorted view as to what the review actually found. An example of a structured abstract that is more forthcoming on Limitations is that on Sleep Apnea .. limitations – “Very few trials evaluated objective clinical outcomes. Data were meager for many specific questions. Studies were generally of moderate to poor quality, and often had short followups, high dropout rates, and poor analyses and reporting.	Thank you - as we have made edits to the report subsequent to peer review, the abstract has also been updated to better reflect the findings and limitations in the report. Unfortunately, the abstract is limited in its word count so cannot be all inclusive. The executive summary is a more inclusive synopsis of the report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 38	Executive Summary	<p>The conclusions in the abstract do not match the evidence in the rest of the report and perpetuate the discredited idea that CBT and GET are the only possible approaches. This is a disservice to the community of patients with ME/CFS. For example, the conclusion of the abstract reads “CBT and GET have shown some benefit whereas other interventions have insufficient evidence to guide clinical practice. GET appears to be associated with harms in some patients.” This is too strong a statement given that the evidence in Table A is contradictory. CBT/counseling studies have “mainly positive results, but mixed.” GET has positive results, but GET+CBT has no effect. In addition, GET studies had high withdrawals due to harms.” In addition, on page 27 “There is low strength evidence, based on 14 trials, that CBT, either group or individual; self-instruction booklets; pragmatic rehabilitation; peer-to-peer counseling; and symptom consultation provide improvement in fatigue, function, quality of life, and employment in adult patients with ME/CFS.” And on page 31: “In summary most trials of CBT or other counseling techniques suggested improvement in overall functioning and fatigue symptoms in ME/CFS patients though in a trial that followed individuals up 5 years after counseling, this affect was no longer seen.” Finally, on page 32, Figure 3. Only three studies show a statistically significant improvement on the SF-36 scale, Deale et al. (1997) (used Oxford definition), and two by White et al. (2011) (PACE Trial, used Oxford definition). The Oxford definition is much too broad, requiring only fatigue to diagnose ME/CFS, and includes people with other fatiguing illnesses, including depression.</p> <p>Please revise the statements in the abstract about CBT and GET to reflect the actual findings in the report.</p>	<p>Thank you for your comments. We agree that the conclusions to the abstract were too cursory and have edited the conclusions.</p>
Public Reviewer # 38	Executive Summary	<p>The conclusion of the abstract states “...negative effects of being given a diagnosis of ME/CFS appear to be more universal.” This seems like odd wording and gives the impression that doctors should not diagnose ME/CFS. In fact the entire “Key Question 1c. What harms are associated with diagnosing ME/CFS?” seems strange. There are many negatives associated with having a debilitating and chronic illness with no known cause, no treatment and no cure, but, in my experience, receiving the diagnosis is a relief. I have two teenagers with ME/CFS, and having a diagnosis of ME/CFS was very helpful in dealing with school authorities who, prior to the diagnosis, insisted that I was a bad parent and my kids were shirking school.</p> <p>Please revise this statement in the abstract to reflect the fact that it is having the illness causes problems, not receiving the diagnosis.</p>	<p>Thank you for your comments. We have added discussion in the full report as evidence allowed on the benefit of receiving a diagnosis of ME/CFS, and we have also revised our conclusion statement.</p>

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Public Reviewer # 38	Executive Summary	Page ES-1 "Uncertainty persists regarding the etiology and whether the condition reflects a single pathologically discrete syndrome, subsets of the same illness, or a nonspecific condition shared by other disease entities." The end of this sentence is an old and discredited view of ME/CFS. Researchers in the field recognize that ME/CFS is a separate, organic illness. Please delete the end of this sentence.	Thank you - we have expanded our introduction to include patient and expert opinion regarding ME vs. CFS.
Public Reviewer # 38	Executive Summary	Page ES-3 (also page 2) "Childhood ME/CFS is uncommon..." This is not true. Childhood ME/CFS has about the same prevalence as adult ME/CFS.	We have added pediatric prevalence information to the introduction.
Public Reviewer # 38	Executive Summary	Page ES-25 (also page ES-2, page 2, page 19, page 60) "Evidence suggests that carrying an ME/CFS diagnosis is associated with perceived stigma, financial instability, difficulty in social interactions and relationships, and a greater risk of receiving a psychiatric diagnosis." Again, it is not carrying the diagnosis that causes problems, but having a chronic illness. Please consider rephrasing this statement.	Thank you for your comment. We have not compared the experience of this chronic condition with others so cannot comment on its similarity.
Public Reviewer # 38	Executive Summary	Page ES-28 "One study comparing CBT with cognitive therapy, anaerobic exercise, or relaxation found that those patients who remained within their energy envelope (avoided overexertion and under exertion by exerting a comfortable range of energy) had a significant improvement in mean fatigue and functioning scores regardless of treatment arm." This is an important point and should be emphasized. In fact, this would be a better statement for the abstract than the existing and inaccurate one about CBT and GET.	Thank you. We agree that this was an interesting and innovative study. The intent of the abstract is to summarize all studies collectively, but we do report further details on this study in the body of the report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 38	Executive Summary	Page ES-29 (also page 4, page 14, page 77): "We elected to include trials using any pre-defined case definition but recognize that some of the earlier criteria, in particular the Oxford (Sharpe, 1991) criteria, could include patients with 6 months of unexplained fatigue and no other features of ME/CFS." I don't understand this decision. If you think the Oxford definition has serious issues, then you should not give studies using it the same credence as studies using more detailed criteria. Please consider removing or down-weighting the importance of the Oxford criteria studies.	We appreciate that the case definitions are very different and that some are more inclusive than others and may reflect less severe cases or non-cases of ME/CFS as is outlined in the Key Question 1 results in the report. After consultation with the Working Group and Technical Expert Panel, we elected to include all case definitions in the report a priori for several reasons. First, there are very few trials; excluding some of these definitions would limit the evidence even further than is already outlined. Second, the intent was that this could at least provide a foundation to determine what interventions may be effective. Where available, we compared findings using different case definitions to determine if findings were consistent or not across studies. We have expanded the discussion of future research needs to indicate that future studies should perform sensitivity analysis to determine differences between case definitions as well as subgroups of patients that meet different criteria.
Public Reviewer # 38	Executive Summary	Page ES-30 "Across all intervention trials, heterogeneity in the population samples (different case definitions used for inclusion), outcomes evaluated, and tools used to measure these outcomes, limited the ability to synthesize data. Acceptance of a single case definition and development of a core outcome set would aide in better studying the interventions to allow for more meaningful guidance for clinicians, policy makers, and patients." This is an important point. One thing that would help with arriving at a single case definition would be to find biological markers for ME/CFS. There is quite a bit of promising research and it is very strange that none of it was included in this review. In fact it was deliberately excluded as relating to etiology and not to diagnosis. It is too late to revise the scope of this review, but hopefully future reviews will include studies searching for biomarkers that might lead to better diagnostic criteria.	Thank you for your comment. We recognize that the biomarker studies may eventually provide insight into the etiology and potentially the diagnosis of ME/CFS, but this work is still in its infancy for diagnosing the syndrome of ME/CFS and has not been studied in a way that reports diagnostic validity in patients with diagnostic uncertainty; therefore, most biomarker studies did not meet inclusion criteria for this report.

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Public Reviewer # 38	Executive Summary	<p>Typos: Page ES-9: "diagnostic uncertainly" should read "diagnostic uncertainty" Page ES-26 and page 70: missing closing quotation mark on "combination of symptoms and signs which have been observed to occur together so frequently and to be so distinctive that they constitute a recognizable clinical picture."</p>	Thank you – these have been addressed.
Marj van de Sande Co-Author/co-editor, ICC and ICP	Executive Summary	<p>Clarification: The International Consensus Criteria (ICC) advocate moving away from the term CFS in favor of ME for those patients meeting the widespread inflammation and multisystemic neuropathy that are characteristic of the underlying pathophysiology of myalgic encephalomyelitis. However, the International Consensus Criteria do NOT advocate embracing the two terms as synonymous. The ICC point out the confusion and problems that have arisen from using broadly inclusive criteria that do not discriminate ME patients from those with other fatiguing conditions. The ICC advocate, "Individuals meeting the International Consensus Criteria should be removed from the Reeves empirical criteria and National Institute for Clinical Excellence (NICE) criteria for chronic fatigue syndrome". (1, page 334) The International Consensus Panel provides further clarification for the need to remove ME patients from the CFS umbrella in MYALGIC ENCEPHALOMYELITIS – Adult & Paediatric: International Consensus Primer for Medical Practitioners. (2) "Misperceptions have arisen because the name 'CFS' and its hybrids ME/CFS, CFS/ME and CFS/CF have been used for widely diverse conditions... There is a poignant need to untangle the web of confusion caused by mixing diverse and often overly inclusive patient populations in one heterogeneous, multi-rubric pot called 'chronic fatigue syndrome'.... Our panel strongly recommends that only the name 'myalgic encephalomyelitis' be used to identify patients meeting the [International Consensus Criteria] ICC because a distinctive disease entity should have one name. Patients diagnosed using broader or other criteria for CFS or its hybrids (Oxford, Reeves, London, Fukuda, CCC, etc.) should be reassessed with the ICC. Those who fulfill the criteria have ME; those who do not would remain in the more encompassing CFS classification.... Not only does it make sense to extricate ME patients from the assortment of conditions assembled under the CFS umbrella, it is compliant with the WHO classification rule that a disease cannot be classified under more than one rubric. The panel is not dismissing the broad components of fatiguing illnesses, but rather the ICC are a refinement of patient stratification. As other identifiable patient sets are identified and supported by research, they would then be removed from the broad CFS/CF category." (emphasis added) (2, page ii)</p>	Thank you for your clarification. We have reviewed the ICC again and have edited the report to reflect their preference of the term ME. We have continued to use the label ME/CS throughout the report in accordance with the P2P workshop.

Commentator & Affiliation	Section	Comment	Response
Marj van de Sande Co-Author/co-editor, ICC and ICP	Executive Summary	<p>(continued) 1. Carruthers BM, van de Sande MI, De Meirleir KL, Klimas DG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Baumbarten-Austrheim B, Bell DS, Carlo-Stella N, Chia J, Darragh A, Jo D, Lewis D, Light AR, Marshall-Gradisbik S, Mena I, et al. Myalgic encephalomyelitis: International Consensus Criteria. J Intern Med 2011; 270: 327-338. [PMID: 21777306] http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02428.x/pdf</p> <p>2. Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Bell DS, Carlo-Stella N, Chia J, Darragh A, Gerken A, Jo D, Lewis D, Light AR, Light K, Marshall-Gradisnik S, McLaren-Howard J, Mena I, Miwa K, Murovska M, Steven S. Editors: Carruthers BM, van de Sande MI. MYALGIC ENCEPHALOMYELITIS – Adult & Paediatric: International Consensus Primer for Medical Practitioners. 2012. ISBN 978-0-9739335-3-6 www.name-us.org/DefintionsPages/DefinitionsArticles/2012_ICC%20primer.pdf</p>	Thank you for your clarification. We have reviewed the ICC again and have edited the report to reflect their preference of the term ME. We have continued to use the label ME/CS throughout the report in accordance with the P2P workshop.
Public Reviewer # 7	Executive Summary	<p>The Draft Report states that: "We elected to include trials using any predefined case definition but recognize that some of the earlier criteria, in particular the Oxford (Sharpe, 1991) criteria, could include patients with 6 months of unexplained fatigue and no other features of ME/CFS. This has the potential of inappropriately including patients that would not otherwise be diagnosed with ME/CFS and may provide misleading results."</p> <p>This rather important caveat should be given greater prominence in the overall report and any summary if it is a fundamental problem which could undermine the conclusions of the entire review.</p>	We appreciate that the case definitions are very different and that some are more inclusive than others and may reflect less severe cases or non-cases of ME/CFS as is fully outlined in the Key Question 1 results of the report. After consultation with the Working Group and Technical Expert Panel, we elected to include all case definitions in the report a priori for several reasons. First, there are very few trials; excluding some of these definitions would limit the evidence even further than is already outlined. Second, the intent was that this could at least provide a foundation to determine what interventions may be effective. Where available, we compared findings using different case definitions to determine if findings were consistent or not across studies. We have expanded the discussion of future research needs to indicate that future studies should perform sensitivity analysis to determine differences between case definitions as well as subgroups of patients that meet different criteria.

Commentator & Affiliation	Section	Comment	Response
Solve ME/CFS Initiative and Research Advisory Council	Executive Summary	The Solve ME/CFS Initiative and our Research Advisory Council thank the Evidence--Based Practice Center and AHRQ for preparing this report and for the attention to detail in the comprehensive review of the literature. Below we have provided specific areas of comment and correction in the suggested format for the authors to consider as they finalize this document. Structured Abstract On page vi of the conclusions in the structured abstract, either list all interventions that showed benefit or state simply that there are several interventions that showed benefit. The conclusions should not list only CBT and GET as beneficial.	Thank you - we have revised our conclusions summary to be more reflective of the complete report results.
Public Reviewer # 38	Executive Summary	Page ES-26 (also Table 7, page 75) "Patients with ME/CFS report feeling stigmatized by their diagnosis in terms of financial stability, work opportunities, perceived judgments on their character, social isolation, and interactions with the health care system." Again, it is not carrying the diagnosis that causes problems, but having a chronic illness. Please consider rephrasing this statement.	Thank you - we have expanded our discussion of harms and potential benefits of receiving a diagnosis of ME/CFS.
Public Reviewer # 1	Executive Summary	Omissions Include i) ES 29 and p. 77 Applicability: "Several features limit its generalizability to the broader population of patients with ME/CFS, including factors surrounding the diagnosis itself." ii) Insufficiency in the conclusions should include -- ES 29 and p. 77 Implications for Clinical and Policy Decisionmaking -- "the limitations in applicability as well as the limitations of the evidence base make it difficult to draw firm conclusions with implications for clinical practice" iii) They should also include -- "Because of limitations in the evidence base, we did not have high confidence in any of the findings from this review [regarding treatment?? or all]" iv) It would be helpful if the abstract also stated what the review did along the lines as is noted in ES-2 "It identifies areas of future research needed to better inform the diagnostic process and treatment strategies."	Thank you for your comments. We have edited the executive summary and abstract to clarify the limits of the report as well as highlight the purpose more clearly.
Peer Reviewer #2	Introduction	Page 9, Line 13: Other expert conceptual work has built the logical argument for post-exertional malaise as a distinctive hallmark of chronic fatigue syndrome, as well: Davenport TE, Stevens SR, VanNess MJ, Snell CR, Little T. Conceptual model for physical therapist management of chronic fatigue syndrome/myalgic encephalomyelitis. Phys Ther. 2010;90(4):602-614. PMID: 20185614.	This reference was reviewed and used to inform our understanding of background information.
Peer Reviewer #2	Introduction	Page 9, Line 56: Consider providing the timeframe for prevalence as a rate, because it is unclear from the current text.	We have updated the information on prevalence and have added a timeframe.
TEP Reviewer #4	Introduction	A good overview of the issues surrounding the diagnosis and treatment of CFS/ME is presented.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	Introduction	While none of the authors are subject matter experts is it clear that consideration was given to the TEP members ie "Experts consider post-exertional malaise (PEM) and memory or concentration problems critical components." Such consideration is greatly appreciated.	Thank you. Our expert panel greatly informed our understanding of the condition and factors to consider in our approach to the report.
Peer Reviewer #4	Introduction	the GET results are superficial and meaningless, in fact the ill effect of GET was completely overlooked The CBT benefit were not analysed in a scientific manner, no Karnofsky scores were quoted in either case. The paper was written to substantiate a flawed CBT/ GET protocol that has been shown to be non effective in various critical assessments	Thank you for your comments. We developed our scope with input from the Working Group and our Technical Expert Panel. We have reported the results that were reported in the trials. There were a few trials that reported the Karnofsky Performance Scale and those are reported in our results section when applicable.
Peer Reviewer # 5	Introduction	I do not have any problems with the introduction. It describes the current sad state of ME/CFS definitions and diagnosis and introduces the tasks the authors carried out.	Thank you for your comments.
TEP Reviewer #6	Introduction	Generally a good overview of ME/CFS issues. The authors do seem to get that this is a complicated and frustrating condition and I commend them for it.	Thank you.
David Egan	Introduction	The "term ME was first used in the 1930s after an outbreak of neuromyesthenia" is a lie and factually wrong. ME was first used to define the illness by Dr.Donald Acheson in the Lancet medical journal in 1955 and has been used ever since- Outbreak at the Roval Free. E.D Acheson. The lancet, Volume 266,Issue 6886,Pages 394- 395, 20 August 1955.	Thank you for informing the historical perspective. We have changed the text accordingly: "Although reports of similar symptom clusters date back to the 1930s, the term myalgic encephalomyelitis (ME) was first used to describe the condition in the 1950s and was recognized by the World Health Organization in the 1960s. The term chronic fatigue syndrome (CFS) was coined in the 1980s after research failed to identify a clear viral association with what was previously labeled chronic Epstein-Barr virus syndrome. Other terms such as post viral fatigue syndrome and chronic fatigue immune dysfunction syndrome have been used in an attempt to associate the syndrome with possible underlying etiologies."

Commentator & Affiliation	Section	Comment	Response
David Egan	Introduction	"CFS was first coined in the 1980s". The term 'CFS' was used to describe an ME outbreak in lake Tahoe in the mid 1980's. The very term 'CFS' is misleading and unscientific, and this was deliberately done by a Dr. Straus who wished to make ME disappear by using a new invented term 'CFS'. This term was then perverted into an unspecific psychological illness by certain individuals in the CDC and NIH. Dr. Straus' letter to Dr. Fukuda shows an attempt to do this, and leave many patients with no proper diagnostics and no proper treatments for a serious biological illness http://www.me-ireland.com/straus/straus.htm This has had serious consequences, including premature death for many patients- http://www.ncf-net.org/memorial.htm ME is ME, it should not have been called 'CFS' or any other name. So let us call ME what it really is 'ME' and diagnose and treat it as a biological illness.	Given that both terms have been used in the literature (both combined and individually), we have elected to use them together as a single term. We have also attempted to shed light on how the case definitions that are associated with these terms may highlight distinct symptom sets (see key question 1).
David Egan	Introduction	"Over the years, there has been disagreement on the underlying etiology and whether the conditions represented by these terms reflect a single pathologically discrete syndrome, subsets of the same illness, or a nonspecific condition shared by other disease entities" This is factually wrong. ME has been well documented since 1955, the WHO classified it in 1969. Please read www.me-ireland.com and learn the facts about ME and outbreaks and epidemics prior to and after 1955.	Thank you - yes, we agree that the syndrome of ME has been well documented over the years. However, the cause (etiology) of the condition remains unknown.
David Egan	Introduction	"The first set of clinical criteria defining the condition were published in 1988" This is factually wrong. The first clinical criteria were described and used by Dr. Acheson in 1959, updated by Dr. Richardson in the early 1960's and by Dr. Ramsey in 1986	Thank you - we have clarified this statement to indicate that the first case definition with an associated set of clinical criteria was published in 1988. We added a comment about the WHO classification in the introduction.

Commentator & Affiliation	Section	Comment	Response
Sister Sandra Duma, OSF, MS Ed	Introduction	<p>Volume 3 Issue 3 of the journal <i>Biology</i> 10.3390/biology3030606 contains an article by David Maughan and Michael Toth entitled “Discerning Primary and Secondary Factors Responsible for Clinical Fatigue in Multisystem Diseases” published on September 22, 2014. These are researchers from the Department of Molecular Physiology and Biophysics from the University of Vermont, Burlington, VT. The article’s abstract states the following:</p> <p>Abstract Fatigue is a common symptom of numerous acute and chronic diseases, including myalgic encephalomyelitis/chronic fatigue syndrome, multiple sclerosis, heart failure, cancer, and many others. In these multi-system diseases the physiological determinants of enhanced fatigue encompass a combination of metabolic, neurological, and myofibrillar adaptations. Previous research studies have focused on adaptations specific to skeletal muscle and their role in fatigue. However, most have neglected the contribution of physical inactivity in assessing disease syndromes, which, through deconditioning, likely contributes to symptomatic fatigue. In this commentary, we briefly review disease-related muscle phenotypes in the context of whether they relate to the primary disease or whether they develop secondary to reduced physical activity. Knowledge of the etiology of the skeletal muscle adaptations in these conditions and their contribution to fatigue symptoms is important for understanding the utility of exercise rehabilitation as an intervention to alleviate the physiological precipitants of fatigue.</p> <p>This brings to mind several points. IF myalgic encephalomyelitis (ME) is a subtype of Chronic Fatigue Syndrome (CFS), which I don’t believe it is, then so should be any and all acute and chronic diseases in which fatigue is a common symptom, such as cancer, multiple sclerosis, heart failure, obstructive pulmonary disease, lupus, AIDS and so on. I have never seen Cancer/CFS or MS/CFS. Neither have I ever seen CBT and GET touted as the main, central, effective treatment for any of these diseases, except for the disease ME. I don’t think cancer patients, their families, and the general public would tolerate the only treatment options available to them being CBT and GET, no matter how cost effective that might be, in spite of the fact that it certainly would not be very therapeutically effective. No, the government has put billions of dollars into researching these diseases so that at this point in time they have treatment options available to them. Unfortunately, that is not the case with ME, which, throughout its history, has received a mere pittance in research dollars. Consequently, there are no treatment options available for ME. This makes this P2P study rather lame. This insufficiency and lameness is what the P2P report should have pointed out. Instead it produced a report with many flaws:</p> <p>1) The failure to be clear and specific about what disease was being studied</p>	<p>Given that both terms have been used in the literature (both combined and individually), we have elected to use them together as a single term. We have also attempted to shed light on how the case definitions that are associated with these terms may highlight distinct symptom sets (see key question 1). Additionally, we have added language in the introduction, discussion, and future research areas of the report to acknowledge the desire of the ME/CFS community and patients to adopt the term ME rather than CFS, which is considered too non-specific a term.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 39	Introduction	<p>A brief examination of the Executive Summary section of the Draft Comparative Effectiveness Review "Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)," prepared for the Agency for Healthcare Research and Quality (AHRQ) and published online September 22, 2014, reveals glaring factual and conceptual errors raising serious questions of the authors' qualifications and the fitness of their Review for its intended purpose. The Review is to be used as an allegedly objective knowledge base for the panel of non-experts at the upcoming Pathways to Prevention (P2P) Workshop on "ME/CFS."</p> <p>The first paragraph of the Background section of the Executive Summary on page ES-1 states:</p> <p>Myalgic encephalomyelitis (ME) and/or chronic fatigue syndrome (CFS) is a condition characterized by chronic and disabling fatigue as well as various additional manifestations including pain, sleep disturbance, neurological and cognitive changes, motor impairment, and altered immune and autonomic responses. [1-3] Experts consider post-exertional malaise (PEM) and memory or concentration problems critical components. [4] [Superscript reference numbers of the original are shown here in brackets.]</p> <p>These are the references cited in the paragraph:</p> <ol style="list-style-type: none"> 1. Carruthers BM, Jain AK, de Meirleir KL, et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. J Chronic Fatigue Syndr. 2003;11(1): 7-115. 2. Carruthers BM, van de Sande MI, De Meirleir KL, et al. Myalgic encephalomyelitis: International Consensus Criteria. J Intern Med. 2011;270(4): 327-38. PMID: 21777306. 3. Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med. 1994;121(12): 953-9. PMID: 7978722.7. 4. Jason LA, Brown A, Evans M, et al. Contrasting chronic fatigue syndrome versus myalgic encephalomyelitis/chronic fatigue syndrome. Fatigue. 2013;1(3)PMID: 23914329. <p>The use of the term "Myalgic encephalomyelitis (ME) and/or chronic fatigue syndrome (CFS)" raises some basic questions. The term presupposes an identity and common referent for the terms "ME" and "CFS" at the outset of the Review which is belied by one of the very references cited. Reference 2 is the 2011 Myalgic Encephalomyelitis: International Consensus Criteria (ME ICC) (Carruthers, 2011) developed by a highly qualified international panel of experienced doctors and biomedical researchers. The IC panel clearly states that ME and CFS should not be used to refer to the same condition, and further states that ME is not characterized by "chronic and disabling fatigue," as claimed by the Review authors.</p>	<p>We have reviewed the consensus panel statement and have edited the report text accordingly:</p> <p>"The most recent international consensus report advocates moving away from the term CFS in favor of the term ME to better reflect an underlying pathophysiology involving widespread inflammation and neuropathology, and to embrace the two terms as synonymous. This panel of experts suggests that ME is a distinct illness inaccurately represented by the broader criteria of CFS."</p> <p>And:</p> <p>"They recommend that patients meeting the International consensus criteria be given the name ME, and that those only meeting the criteria for CFS remain classified as CFS."</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 39	Introduction	<p>(continued) The ME ICC state: Using 'fatigue' as a name of a disease gives it exclusive emphasis and has been the most confusing and misused criterion. No other fatiguing disease has 'chronic fatigue' attached to its name – e.g. cancer/chronic fatigue, multiple sclerosis/chronic fatigue – except ME/CFS. Fatigue in other conditions is usually proportional to effort or duration with a quick recovery and will recur to the same extent with the same effort or duration that same or next day. The pathological low threshold of fatigability of ME described in the following criteria often occurs with minimal physical or mental exertion and with reduced ability to undertake the same activity within the same or several days. (Carruthers, 2011, page 328) The ME ICC characterize ME this way: Myalgic encephalomyelitis is an acquired neurological disease with complex global dysfunctions. Pathological dysregulation of the nervous, immune and endocrine systems, with impaired cellular energy metabolism and ion transport are prominent features. Although signs and symptoms are dynamically interactive and causally connected, the criteria are grouped by regions of pathophysiology to provide general focus. (Carruthers, 2011, page 329) In no legitimate way can this statement be construed to mean the subjective symptom of "fatigue." The ME ICC do not even list chronic fatigue as a necessary symptom for an ME diagnosis, let alone as a characterizing feature of the disease. It is a gross misrepresentation for the Review authors to cite the ME ICC as a reference for their misleading contention that ME and CFS refer to the same condition "characterized by chronic and disabling fatigue." Using the ME ICC as a reference for this contention displays either an unfamiliarity with the cited reference or a deliberate attempt to mischaracterize the reference to support a contested statement when, in fact, the reference contradicts the statement. Such carelessness, at best, or intellectual dishonesty, at worst, should be sufficient disqualification for these authors as a source of accurate, reliable, and objective information. Furthermore, the concluding sentence of the paragraph states, "Experts consider post-exertional malaise (PEM) and memory or concentration problems critical components. [4]" Reference 4 is a secondary, social science paper that again does not support the contention of the Review authors. Going to the primary definitional sources cited by the Review and used in Reference 4, Reference 1 is the 2003 Canadian Consensus Criteria for ME/CFS (CCC) (Carruthers, 2003). The CCC do not just consider PEM to be a "critical component," but more specifically an essential, necessary symptom for an ME/CFS, the term used by the CCC, diagnosis. Reference 3, the 1994 Fukuda case definition of CFS, lists PEM as one of eight optional symptoms for a CFS diagnosis – hardly a "critical component." Reference 2, the ME ICC, objects to the term "post-exertional malaise" (PEM) altogether:</p>	<p>We have reviewed the consensus panel statement and have edited the report text accordingly: "The most recent international consensus report advocates moving away from the term CFS in favor of the term ME to better reflect an underlying pathophysiology involving widespread inflammation and neuropathology, and to embrace the two terms as synonymous. This panel of experts suggests that ME is a distinct illness inaccurately represented by the broader criteria of CFS." And: "They recommend that patients meeting the International consensus criteria be given the name ME, and that those only meeting the criteria for CFS remain classified as CFS."</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 39	Introduction	<p>(continued)'Malaise' – a vague feeling of discomfort or fatigue [41] – is an inaccurate and inadequate word for the pathological low-threshold fatigability and postexertional symptom flare. Pain and fatigue are crucial bioalarm signals that instruct patients to modify what they are doing in order to protect the body and prevent further damage. Postexertional neuroimmune exhaustion [PENE] is part of the body's global protection response and is associated with dysfunction in the regulatory balance within and between the nervous, immune and endocrine systems, and cellular metabolism and ion transport [42–46]. The normal activity/rest cycle, which involves performing an activity, becoming fatigued and taking a rest whereby energy is restored, becomes dysfunctional. [See the original paper for references cited.] (Carruthers, 2011, page 331)</p> <p>Again, within a single paragraph, the Review authors have either carelessly or deliberately mischaracterized references to support questionable claims.</p>	<p>We have reviewed the consensus panel statement and have edited the report text accordingly:</p> <p>"The most recent international consensus report advocates moving away from the term CFS in favor of the term ME to better reflect an underlying pathophysiology involving widespread inflammation and neuropathology, and to embrace the two terms as synonymous. This panel of experts suggests that ME is a distinct illness inaccurately represented by the broader criteria of CFS."</p> <p>And:</p> <p>"They recommend that patients meeting the International consensus criteria be given the name ME, and that those only meeting the criteria for CFS remain classified as CFS."</p>
Peer Reviewer #3	Introduction	The Introduction is the best part of this flawed review.	We are grateful that the background was informative as it is designed to provide a framework for the report. The evidence report follows a systematic process with pre-defined inclusion criteria and thus may not be as inclusive as the introduction.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 40	Introduction	<p>The British versions began with elaborate theorizing rather than the empirical data, however paltry, that the American naming had relied on. Their theory asserts that “false beliefs” and “deconditioning” lay behind the complaints of unwellness accompanied by fatigue which Britain’s general practitioners (GPs) were likely to hear. The theorizing sprung fully formed from a psychiatrist’s imagination, rather like Athena from Zeus’ head. While quite legally appropriating the untrademarked name of Chronic Fatigue Syndrome, they named two new definitions for their creation “Oxford Definition” and “London Definition.”</p> <p>The AHRQ Evidence Review must reflect that neither is to be considered in any way synonymous with the “Chronic Fatigue Syndrome” derived from the Incline Village outbreak of Myalgic Encephalomyelitis, and laid out, albeit imperfectly, in the Fukuda definition.</p> <p>The U.K. - invented definitions of “CFS” do not involve immune dysfunction, neurological symptoms, infections, sore throats, swollen glands, new headaches, or myalgias, all of which are cited in the U.S. disease. Most important, they do not recognize Post-exertional Malaise (PEM.) Mainly it seems they are characterizing clinical depression not previously diagnosed. ...</p>	<p>Thank you for your comments. We have highlighted the differences in case definitions in the results for Key Question 1 as well as reviewed what is available about how patients and/or providers experience the name/label, as well as the diagnosis. Your historical perspective has been very enlightening.</p>
Public Reviewer #2	Introduction	<p>Firstly, a brief apology for not being as thorough and well researched in my comments as I would like, and the clumsy structure of my response. I have only been able to look in detail at a couple of areas, and I am concerned that the limited time provided for comments on this draft may lead to important issues going unaddressed</p> <p>I hope that this is only the beginning of a process which will provide further time for discussion and debate as the review develops. The political and social context around ME/CFS needs to be addressed, particularly as part of any attempt to assess the costs and benefits of biopsychosocial approaches to the management of patients, and this requires extra work and care from those conducting any review, certainly in comparison to an assessment of the efficacy of a pharmaceutical intervention which can be assessed in double-blind trials.</p>	<p>We have attempted to outline the social context of the condition and how it affects patients, but it is beyond the scope of this report to consider the political context as it may exist as well as specific financial costs. We have endeavored to relay the benefits and harms of treatments clearly and in an unbiased manner.</p>

Commentator & Affiliation	Section	Comment	Response
Kartik A. Parekh	Introduction	<p>AHRQ appears to have borrowed the combination term "ME/CFS" from NIH, which has quite recently begun using "ME/CFS" to mean the sum of any and all disease descriptions that include the terms CFS or ME, without any rationale for the inclusion of all such descriptions under a single clinical label, and lacking any formal or informal definition, let alone any kind of validation. The only truly formal use of the term "ME/CFS" was by the 2003 Canadian Consensus document [6], which sought to identify a legitimate clinical entity, as close as possible to previously described ME, from the excessively non-specific CFS constructs, while - perhaps unwisely - compromising on terminology. The term ME/CFS is also often used informally by clinicians, researchers, advocacy groups and patients for pragmatic purposes and to try to raise awareness of ME while acknowledging that ME is rarely given as a diagnosis in countries such as the United States, where most patients who better satisfy ME criteria have been diagnosed with CFS instead. ...</p> <p>In the interests of scientific rigor and proper disease surveillance, NIH/HHS must not conflate established case definitions that have not been demonstrated to describe the same clinical entity. The primary inadequacy of the AHRQ report is the a priori nosological and semantic error of conceptually subsuming ME within the CFS diagnostic construct without sufficient validation.</p> <p>Absent a drastic revision of its current draft report that would reflect a real understanding of these fundamental nosological issues, I urge AHRQ to inform NIH that it cannot participate in P2P, nor publish an evidence review, on scientific and ethical grounds .</p>	<p>Given that both terms have been used in the literature (both combined and individually), we have elected to use them together as a single term. We have also attempted to shed light on how the case definitions that are associated with these terms may highlight distinct symptom sets (see key question 1). Additionally, we have added language in the introduction, discussion, and future research areas of the report to acknowledge the desire of the ME/CFS community and patients to adopt the term ME rather than CFS, which is considered too non-specific a term.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 1	Introduction	<p>Opinion of experts important and should be considered at this stage of development, not ruled out because of an “inherent risk of bias”. The potential for bias should be noted but work not entirely discounted as a result. (Cross reference to Comment one dealing with case definition)</p> <p>Reference in Review -- ES-29 “Given that the condition is a syndrome with a constellation of symptoms and lacking a gold standard for diagnostic comparison, it is at inherent risk of bias by the opinion of experts.”</p> <p>Discussion – Attempts to minimize bias may inadvertently have resulted in important information being ignored or downplayed.</p> <p>In spite of an attempt to undertake the review impartiality through extraction of the evidence to tables (which are then carefully compared) inconsistencies and gaps arise. Many studies trying to bridge distance between case definitions (pattern recognition) and the biological underpinnings.</p> <p>Scadding JG. Diagnosis: the clinician and the computer (Ref. 117 (p. 90) Lancet. 1967;2((7521):877-82 PMID: 4168324) is used as a reference for the term ‘syndrome’: “a combination of symptoms and signs which have been observed to occur together so frequently and to be so distinctive that they constitute a recognizable clinical picture.” The Scadding reference also discusses the natural evolution from the use of pattern recognition to one that is more rules-based [And, more amenable to the strict evidence-based medicine approach.]</p> <p>The evolution noted by Scadding has been described more recently by authors Clayton Christensen, Jerome Grossman and Jason Hwang in their book, The Innovator’s Prescription: A Disruptive Solution to Health Care. McGraw Hill 2008. They see an evolution from “intuitive medicine” using and needing highly trained professionals to “empirical medicine.”</p> <p>p. xxii “When precise diagnosis isn’t possible, then treatment must be provided through intuitive medicine, where highly trained and expensive professionals solve medical problems through intuitive experimentation and pattern recognition. As patterns in these patients become clearer, care evolves into the realm of evidence-based, or empirical medicine – where data is amassed to show that certain ways of treating patients are, on average, better than others. Only when diseases are diagnosed precisely, however, can therapy that is predictably effective for each patient be developed and standardized. We term this domain precision medicine.”</p>	<p>Thank you for your comment. We have included in our introduction and discussion references that otherwise would not have met our inclusion criteria to hopefully provide a more inclusive impression of the ME/CFS community and their perspectives. That said, the approach to the evidence for our results is scientifically based and follows a strict methodological protocol that does not include opinion pieces.</p>
Public Reviewer # 41	Introduction	The top 10 tests for MECFS have already been determined in Canada.	Thank you - we have reviewed these.

Commentator & Affiliation	Section	Comment	Response
Trinka Schneider on behalf of Public Reviewer # 39	Introduction	I concur with and request the input at the following Occupy CFS webpage listed below be incorporated before any draft is finalized. At the UN CRPD Ad Hoc Committee the theme Nothing about us without us was lifted up as a gold standard for incorporating patient expert CFS clinicians and researchers as well as NGO input into any drafting process. We should not do any less.	Thank you for your comments. We have reviewed the OccupyCFS website and attempted to share some of the perspectives of patients and advocacy groups in our introduction, discussion, and future research needs sections.
Solve ME/CFS Initiative and Research Advisory Council	Introduction	Introduction On page 2, last sentence of 1st paragraph, "Economic impact is considerable with most adult patients never returning to work." the original economic impact papers (there are 3) should be cited rather than these review articles.	Thank you - this information was obtained from the review paper, so we have continued to cite it as our source.
Solve ME/CFS Initiative and Research Advisory Council	Introduction	On page 1, 3rd paragraph of the Introduction, it indicates that few if any risk factors have been identified. However, there are several published epidemiology, birth cohort, twin and primary care studies that have identified risk markers including being female, recent viral infection, genetic vulnerability and family history. All of these provide important and potential diagnostic clues for ME/CFS and while excluded from the review, should at least be noted in the Introduction.	Thank you - we have expanded our discussion of this section but reiterate that although associations have been noted, no definitive risk factor has been identified.
Solve ME/CFS Initiative and Research Advisory Council	Introduction	On page 1 of the Introduction it is stated, "This review is not intended to address the question of etiology nor underlying factors that lead to the onset or perpetuation of ME/CFS but rather to focus on the diagnosis and treatment of this syndrome." • It would be helpful to clarify how diagnosis is possible without understanding the cause or perpetuating factors of ME/CFS. We believe what is intended here is to help the reader understand that the review will focus on evidence using symptoms for diagnosis versus objective markers (since none have been validated) or possible causes (since no causal factors have been confirmed). The last sentence of the Introduction on page 2, "This report is not intended to be used or likely to be useful to develop criteria for disability or insurance" somewhat contradicts what is stated on page ii, "The final report (not draft) may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies" and should be clarified/corrected.	Thank you for your comments. ME/CFS is challenged by the lack of understanding regarding etiology and lack of a reference standard for diagnosis. We have expanded our discussion of diagnosis when a reference standard does not exist and discussed the limitations that this presents. We have clarified in the methods section that we are not considering intermediate outcomes such as biomarkers for measures of treatment effectiveness given that there remains uncertainty as to the meaningfulness of these findings. The comment regarding basis for reimbursement and coverage policies is a disclaimer by AHRQ rather than an endorsement that it should be used as such. We have expanded the text to indicate that it is not intended for this use.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 52	Introduction	I feel that the inclusion of the Oxford definition in your review is a fatal flaw that will render your efforts at best meaningless and at worst harmful to those with MECFS.	We have outlined the differences between case definitions in key question 1 but have elected to include all case definitions in the report a priori with the intent that the evidence could at least provide a review of what is currently known and the limitations of this research in order to provide guidance for future research. Where available, we compared findings using different case definitions to determine if findings were consistent or not across studies. . We have expanded our discussion of the limitations, applicability and future research to highlight the need for subgroup analysis to determine how different populations may respond. Additionally, we have edited our report to highlight any differences noted when different case definitions are used; It was our intent to err on the side of including important and/or informative evidence from earlier studies and to also highlight differences if differences exist.
Public Reviewer # 42	Introduction	Executive Summary page vi whereas the negative effects of being given a diagnosis of MECFS appear to be more universal This is an ambiguous statement I read it as if a patient is diagnosed with MECFS it makes them worse in some way whereas what it actually refers to Page ES11 is the stigma and medical prejudice patients experience.	Thank you for this comment. We have changed the conclusion statement in each section.
Public Reviewer #3	Introduction	I concur with and request the input at the following Occupy CFS webpage listed below be incorporated before any draft is finalized. At the UN CRPD Ad Hoc Committee the theme Nothing about us without us was lifted up as a gold standard for incorporating patient expert CFS clinicians and researchers as well as NGO input into any drafting process. We should not do any less.	Thank you - we have reviewed the Occupy CFS website. We have included patients on our Technical Expert Panel and have included an expert in the field as a consultant throughout the course of the review.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #43	Introduction	<p>I am 52 years old on medical disability and suffering from Myalgic Encephalomyelitis Chronic Fatigue Syndrome also known as MECFS. I need your help http://www.effectivehealthcare.ahrq.gov/searchforguidesreviewsandreports/pageactiondisplay/Product/productID1976 Here are the SCIENTIFIC articles from just the past MONTH http://www.sciencedirect.com/sciencearticlepii/S1043466614002919 http://www.prohealth.com/mecfs/Inflammatory and oxidative and nitrosative stress cascades as new drug targets in myalgic encephalomyelitis and chronic fatigue syndrome Inflammatory and oxidative and nitrosative stress cascades as new drug targets in myalgic encephalomyelitis and chronic fatigue syndrome A paper discusses drug candidates for ME and CFS which target inflammatory pathways... October 1 2014 High Throughput Sequencing of Plasma MicroRNA in Chronic Fatigue Syndrome Myalgic Encephalomyelitis High Throughput Sequencing of Plasma MicroRNA in Chronic Fatigue Syndrome Myalgic Encephalomyelitis Researchers identify circulating miRNAs from CFSME patients providing a basis for CFSME biomarkers.... September 30 2014 Use of single nucleotide polymorphisms SNPs to distinguish gene expression subtypes of chronic fatigue syndrome myalgic encephalomyelitis CFSME Use of single nucleotide polymorphisms SNPs to distinguish gene expression subtypes of chronic fatigue syndrome myalgic encephalomyelitis CFSME Human SNPs located within CFSME associated genes are associated with particular genomic subtypes of CFSME... September 29 2014 Tryptophan depletion in chronic fatigue syndrome a pilot crossover study Tryptophan depletion in chronic fatigue syndrome a pilot crossover study In a pilot study MECFS patients do not appear to have excessive serotonin levels... September 22 2014 The effect of relaxation therapy on autonomic functioning symptoms and daily functioning in patients with chronic fatigue syndrome or fibromyalgia a systematic review The effect of relaxation therapy on autonomic functioning symptoms and daily functioning in patients with chronic fatigue syndrome or fibromyalgia a systematic review A systematic literature study finds that guided imagery may help relieve pain for some patients... September 12 2014 Overcoming the barriers to the diagnosis and management of chronic fatigue syndrome ME in primary care a meta synthesis of qualitative studies Overcoming the barriers to the diagnosis and management of chronic fatigue syndrome ME in primary care a meta synthesis of qualitative studies Skepticism among health professionals can lead to reluctance to make a diagnosis of MECFS... September 6 2014 Symptoms of autonomic dysfunction in chronic fatigue syndrome Symptoms of autonomic dysfunction in chronic fatigue syndrome An abnormality of dynamic blood pressure regulation is particularly associated with fatigue severity in CFSME...</p>	<p>Thank you for your suggestions. We have reviewed the citations suggested which do not meet the inclusion criteria for this report</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 43	Introduction	(continued) September 5 2014 An exploration of the Impact of Chronic Fatigue Syndrome and Implications for Psychological Service Provision An exploration of the Impact of Chronic Fatigue Syndrome and Implications for Psychological Service Provision A study finds that social support is greatly lacking for sufferers of chronic fatigue syndrome... September 4 2014 Here are other pertinent articles that may interest you What is the current NHS service provision for patients severely affected by chronic fatigue syndromemyalgic encephalomyelitis A national scoping exercise What is the current NHS service provision for patients severely affected by chronic fatigue syndromemyalgic encephalomyelitis A national scoping exercise Study finds limited access to specialist care for patients with severe MECFS... August 27 2014 Characterization of Natural Killer Cell Phenotypes in Chronic Fatigue Syndrome Myalgic Encephalomyelitis Characterization of Natural Killer Cell Phenotypes in Chronic Fatigue Syndrome Myalgic Encephalomyelitis A study characterizes four NK cell phenotypes in CFSME that indicate reduced NK function... July 25 2014 Human herpes virus 6 and the nervous system Human herpes virus 6 and the nervous system HHV6 infects most infants by the age of 2 and has been implicated in many central nervous system CNS diseases ... July 24 2014 Induction of interleukin1B by activated microglia is a prerequisite for immunologically induced fatigue Induction of interleukin 1B by activated microglia is a prerequisite for immunologically induced fatigue Research finds that microglial activation in the brain through the action of the cytokine IL1B induces fatigue.... July 19 2014 Association of mitochondrial dysfunction and fatigue A review of the literature Association of mitochondrial dysfunction and fatigue A review of the literature A review examines studies that investigated the association of markers of mitochondrial dysfunction with fatigue.... July 12 2014	Thank you for your suggestions. We have reviewed the citations suggested which do not meet the inclusion criteria for this report.
Public Reviewer # 43	Introduction	I am 62 years old and have suffered with MECFS since March 1981. I am disabled mostly home bound on oxygen 24/7 walk with a can or walker and have inhome assistance for cooking cleaning grocery shopping etc. I have followed the P2P Systematic Evidence Review process with great interest. I have several concerns with both the methods used to evaluate research and the preliminary results of the complex disease. My ability to provide input is limited by severe Post Exertional Malaise brought on by numerous medical appointments in the past few weeks. But I will try to communicate some of my concerns.	Thank you for sharing your story.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #44	Introduction	I am writing to protest the entire P2P process including the production of this report. I have had ME for 30 years Im homebound cant do anything I have a lot of severe abnormalities mentioned in the scientific ME literature. Im outraged at the US Department of Health Human Services HHS pretense that P2P is responsive to the Chronic Fatigue Syndrome Advisory Committee CFSAC October 2012 recommendation to convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition useful for research diagnosis and treatment. In no way is the P2P process responsive to this recommendation. NIH has not engaged or involved stakeholders in a substantive way. The Workshop panel consists of individuals with no expertise in ME or CFS. It ignores the subsequent letter to HHS by disease experts who have adopted the Canadian Case Definition for research to be updated as needed. Instead the focus of the draft report is medically unexplained fatigue. By using evidence based practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possible worse than what has already been inflicted on people like me. For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purposes.	Thank you for your comments. The evidence report is only part of the P2P workshop. The purpose of the P2P is to identify areas for future research and not to reach a consensus for a case definition.
Public Reviewer # 45	Introduction	I am a patient with MECFS in N.Ireland and I am writing to protest the entire P2P process including the production of this report. I am outraged at the US Department of Health Human Services HHS pretense that P2P is responsive to the Chronic Fatigue Syndrome Advisory Committee CFSAC October 2012 recommendation to convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition useful for research diagnosis and treatment. In no way is the P2P process responsive to this recommendation. NIH has not engaged or involved stakeholders in a substantive way. The Workshop panel consists of individuals with no expertise in ME or CFS. It ignores the subsequent letter to HHS by disease experts who have adopted the Canadian Case Definition for research to be updated as needed. Instead the focus of the draft report is medically unexplained fatigue. By using evidence based practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possible worse than what has already been inflicted on people like me. For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purposes.	We are sorry to hear about the debilitating effects experienced and hope that future research will provide guidance for more effective diagnosis and treatment options. Although the organization of the P2P workshop and process is beyond the scope of this report, one of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded on this in the discussion section. We have also highlighted the differences between case definitions and how this affects the types of patients included in studies.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 46	Introduction	<p>My concerns as expressed through occupyCFS.com Evidence about the significant differences in patient populations and in the unreliability and inaccuracy of some of these definitions was ignored and/or dismissed. This includes Dr. Leonard Jason's work undermining the Reeves Empirical definition a study that shows the instability of the Fukuda definition over time in the same patients studies demonstrating that Fukuda and Reeves encompass different populations and differences in inclusion and exclusion criteria especially regarding PEM and psychological disorders. Diagnostic methods were assessed without first establishing a valid reference standard. Since there is no gold reference standard each definition was allowed to stand as its own reference standard without demonstrating it was a valid reference. Critical biomarker and cardiopulmonary studies some of which are in clinical use today were ignored because they were judged to be intended to address etiology regardless of the importance of the data. This included most of Dr. Snells and Dr. Kellers work on two day CPET Dr. Cooks functional imaging studies Dr. Gordon Brodericks systems networking studies Dr. Klimass and Dr. Fletchers work on NK cells and immune function and all of the autonomic tests. None of it was considered. Treatment outcomes associated with all symptoms except fatigue were disregarded potentially resulting in a slanted view of treatment effectiveness and harm. This decision excluded Dr. Lerner's antiviral work as well as entire classes of pain medications antidepressants antiinflammatories immune modulators sleep treatments and more. If the treatment study looked at changes in objective measures like cardiac function or viral titers it was excluded. If the treatment study looked at outcomes for a symptom other than fatigue it was excluded. Treatment trials that were shorter than 12 weeks were excluded even if the treatment duration was therapeutically appropriate. The big exclusion here was the rituximab trial despite following patients for 12 months it was excluded because administration of rituximab was not continuous for 12 weeks even though rituximab is not approved for 12 weeks continuous administration in ANY disease. Many other medication trials were also excluded for not meeting the 12 week mark. Counseling and CBT treatment trials were inappropriately pooled without regard for the vast differences in therapeutic intent across these trials. This meant that CBT treatments aimed at correcting false illness beliefs were lumped together with pacing and supportive counseling studies and treated as equivalent. Conclusions about treatment effects and harms failed to consider what is known about ME and its likely response to the therapies being recommended. This means that the PACE an Oxford study results for CBT and GET were not only accepted despite the many flaws in those data but were determined to be broadly applicable to people meeting any of the case definitions. Data on the abnormal physiological response to exercise in ME patients were excluded and so the Review did not conclude that CBT and GET could be harmful to these patients although it did allow it might be possible.</p>	<p>Thank you for your comments. We have reviewed the occupy CFS website. We appreciate that there is no gold or reference standard for ME/CFS diagnosis and have used accepted methodology with discussion of limitations in our review of this evidence. We have not included intermediate outcomes such as biomarkers and cardiopulmonary studies but have identified that summarizing this data, particularly as it surrounds PEM, is appropriate for a subsequent review. Although we recognize the importance of better understanding PEM, the diagnoses and treatment of individual symptoms of ME/CFS was beyond the scope of the questions designed by the Planning Committee. Other experts will be speaking to these topics at the P2P workshop.</p> <p>The advice of the Technical Expert Panel was that the most meaningful and helpful to focus on the syndrome of ME/CFS and the universally experienced symptom of fatigue. We will recommend areas of future research including a systematic review on PEM diagnosis and treatment which would be a topic unto itself.</p> <p>We appreciate your comment about excluding studies of treatments that were appropriately given for <12 weeks duration and we have performed a subsequent search to identify these studies and have included discussion of them in the report.</p>

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Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 46	Introduction	<p>My concerns as expressed through occupyCFS.com Evidence about the significant differences in patient populations and in the unreliability and inaccuracy of some of these definitions was ignored and/or dismissed. This includes Dr. Leonard Jason's work undermining the Reeves Empirical definition a study that shows the instability of the Fukuda definition over time in the same patient's studies demonstrating that Fukuda and Reeves encompass different populations and differences in inclusion and exclusion criteria especially regarding PEM and psychological disorders. Diagnostic methods were assessed without first establishing a valid reference standard. Since there is no gold reference standard each definition was allowed to stand as its own reference standard without demonstrating it was a valid reference. Critical biomarker and cardiopulmonary studies some of which are in clinical use today were ignored because they were judged to be intended to address etiology regardless of the importance of the data. This included most of Dr. Snells and Dr. Kellers work on two day CPET Dr. Cooks functional imaging studies Dr. Gordon Brodericks systems networking studies Dr. Klimass and Dr. Fletchers work on NK cells and immune function and all of the autonomic tests. None of it was considered. Treatment outcomes associated with all symptoms except fatigue were disregarded potentially resulting in a slanted view of treatment effectiveness and harm. This decision excluded Dr. Lerner's antiviral work as well as entire classes of pain medications antidepressants antiinflammatories immune modulators sleep treatments and more. If the treatment study looked at changes in objective measures like cardiac function or viral titers it was excluded. If the treatment study looked at outcomes for a symptom other than fatigue it was excluded. Treatment trials that were shorter than 12 weeks were excluded even if the treatment duration was therapeutically appropriate. The big exclusion here was the rituximab trial despite following patients for 12 months it was excluded because administration of rituximab was not continuous for 12 weeks even though rituximab is not approved for 12 weeks continuous administration in ANY disease. Many other medication trials were also excluded for not meeting the 12 week mark. Counseling and CBT treatment trials were inappropriately pooled without regard for the vast differences in therapeutic intent across these trials. This meant that CBT treatments aimed at correcting false illness beliefs were lumped together with pacing and supportive counseling studies and treated as equivalent. Conclusions about treatment effects and harms failed to consider what is known about ME and its likely response to the therapies being recommended. This means that the PACE an Oxford study results for CBT and GET were not only accepted despite the many flaws in those data but were determined to be broadly applicable to people meeting any of the case definitions. Data on the abnormal physiological response to exercise in ME patients were excluded and so the Review did not conclude that CBT and GET could be harmful to these patients although it did allow it might be possible.</p>	<p>(continued) We have performed a secondary analysis of only CBT studies and have included this in our report. It is beyond the scope of this report to review underlying etiology, including the theories surrounding why CBT may be effective. We have expanded our discussion of the limitations to the PACE study and others.</p>

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Published Online: December 9, 2014

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 47	Introduction	PROTEST P2P Process on MECFS	Thank you. Noted.
Public Reviewer #5	Introduction	I am a MECFS patient in Sweden. The following are my comments. The draft report I refer to as this study. Thank you for providing the opportunity to comment.	We wish you well and appreciate your comments.
Public Reviewer # 2	Introduction	I am writing to protest the entire P2P process including the production of this report.	Thank you - noted.
Public Reviewer # 48	Introduction	Comments on Draft Report entitled Diagnosis and Treatment of Myalgic Encephalomyelitis Chronic Fatigue Syndrome MECFS By [Public Reviewer # 48] formerly a Certified Financial Planner before being struck down and disabled by M.E. in 2008. 10/2014 See General Comments Below.	Thank you for sharing your story.
TEP Reviewer #2	Methods	The methodology is certainly adequate to the task. No issues with inclusion and exclusion criteria; logical exposition of the text.	Thank you.
TEP Reviewer #3	Methods	With regard to the statistical measures, the authors inform the study using accuracy of classification yet there is no diagnostic gold standard on which to assess accuracy. The authors even state on page ES-10: "There is no diagnostic gold standard for ME/CFS and no studies evaluated the accuracy of current diagnostic methods" And yet accuracy of classification is the very basis of Key Question 1 and the discussion of the neural network classifier proposed by Linder et al. (2002)(ref. 38). If the Fukuda case definition is being used as such a de facto gold standard then this should be stated clearly in the Outcomes section and in the section entitled Data Extraction and Data Management. This is a major flaw in the report.	Thank you for this insightful comment. We have made changes to how we approach the write up for Key Question 1 and have attempted to highlight this lack of gold standard and its implications.
TEP Reviewer #3	Methods	When referring to Key Question 1 in the section entitled Timing, the authors mention that there was not timeline considered. Since the authors report that the spontaneous recovery rate is substantially higher in pediatric cases and that the majority of cases involve female subjects, one could argue that age and/or illness progression play a role in determining the diagnostic signature and that these should be considered.	Thank you - you bring up an interesting point of discussion. When reported, we did attempt to include duration of illness for Key Question 2 but felt that any timing limitations to Key Question 1 may further reduce the available evidence.
Peer Reviewer #2	Methods	Page 12, Line 49: The inclusion criteria for articles address Key Question #1 should include studies that differentiate between individuals with ME/CFS and other forms of fatigue, rather than exclusively focus on articles that compare the clinimetric properties of various classification frameworks for the condition. Also, the expression of study results as clinimetric test properties (i.e., derived from the area under the receiver operating characteristics curve) seems unnecessarily simplistic. The inclusion criteria for articles that address Key Question #1 should include functional sub-classification of ME/CFS	Thank you for this comment. We used the standard outcomes for diagnostic test evaluation studies, which include sensitivity, specificity, and AUC among others. We looked for articles that addressed how subgroups vary (Key Question 1b) but functional sub-classification was not one of the intents of this report.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	Methods	Inclusion criteria was somewhat narrow. With a full text review of only 64 studies included, broadening the search criteria would be instructive. While the introduction acknowledges the critical components from the experts none of these components were used in the selection criteria. The use of fatigue as the only criteria for Key Question 1 diminishes the multi-system nature of the illness and is a limitation, perhaps even a fatal flaw of the report. Please consider expanding the criteria for Key Question 1 to include other important symptom features of the syndrome.	The investigators reviewed 6,175 abstracts and 1,069 full text articles. Unfortunately, only 79 studies (89 publications) met the pre-defined inclusion criteria. A priori, we were commissioned to review the evidence on diagnosing the syndrome of ME/CFS rather than methods used to diagnose specific symptoms such as orthostatic hypotension, PEM, etc. Identifying diagnostic tests for specific symptoms was beyond the scope of this report.
TEP Reviewer #4	Methods	Search strategies are well stated and logical. Criterion for outcome measures is quite narrow. Statistical methods are reasonable.	The outcome measures addressed were pre-defined, and for Key Question 1 were reflective of the utility of the tool as a diagnostic test for the syndrome of ME/CFS. The outcomes for Key Question 2 were pre-defined and focused on patient-centered measures reflective of change in the syndrome of ME/CFS rather than specific symptoms. In consultation with the NIH working group, AHRQ, and the technical expert panel, it was decided to include fatigue as an outcome measure given its universal presence in all case definitions.
Peer Reviewer #3	Methods	As an example of the lack of quality I will focus on the Diagnostics section (other sections have the same problems). Nearly all of the publications reviewed in the Diagnostics section were from second rate journals (impacts less than 2.5) that are not freely available. These studies mostly have very small samples sizes, most much too small to have meaningful ROC analyses, and still included these, and included statistics that were not corrected for multiple comparisons. Further no a priori hypotheses were mentioned and no blinding procedures were in place for nearly all studies reported on. Studies that had AUC mentioned in them were included even when these AUCs were not of ROCs. The AUCs in these studies were nothing but methods used to collapse data collected over different times into one measure in order to decrease the number of measurements to obtain any statistical power. This is commonly used in many of the excluded studies but because AUC was not in the abstracts, they were excluded from review.	Thank you for this comment. The standard approach in an evidence review is to evaluate all applicable literature regardless of journal, and to rate studies as to applicability and quality. If provided with additional studies that reported AUCs we would be happy to review them.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Methods	For the diagnostic methods, while 11 studies were reviewed, many of these were from the same data set from the same group. 8 of the studies were from 3 groups. So, in fact, only 6 groups information was reviewed. Worse, because the same patients were used for more than one of these reports, the sample size is less than half of the apparent size. In all of the exercise studies, for example, the sample sizes are less than 20 for the CFS patients. Given the known subgroups and known heterogeneity in ME/CFS, ROCs cannot be informative with this small a sample size. Validation cannot be done using the same cohort.	We agree that this is a limitation of the published literature. We have revised the text to reflect this.
Peer Reviewer #3	Methods	This section suffered from the lack of discussion of subjective vs. objective diagnostic methods, and the pros and cons of both.	The goal of this report was to review objective methods for diagnosis of ME/CFS
Peer Reviewer #3	Methods	Most biomarker studies were eliminated, apparently without adequate review, since some of these did include diagnostic outcomes using ROC/AUC (the real ones, not the AUC mentioned above) and some of these had adequate sample size, and were tested against other non ME/CFS fatiguing conditions, albeit in later publications, as is almost always the case. The possibility that a series of publications using new patients, and different control populations, some of which might be other fatigued patients and testing a previous diagnostics was apparently not considered. Of course, this is the norm for diagnostic development publications.	The scope of this report was not to review etiology but rather to help inform on aspects of diagnosis and treatment of the syndrome ME/CFS.
Peer Reviewer #3	Methods	Interestingly, while the reviewers adhered to exclusion of publications because they did not meet the letter of the Key questions in most cases, they did decide to include a second group of publications evaluating how the case definitions compare with each other, and whether they identify the same or different populations. This is a useful endeavor, and if more studies were included could be meaningful.	Thank you.
Peer Reviewer #4	Methods	The inclusion and exclusion data were not critically observed, there were a multitude of criteria methods making the comparisons invalid.	The investigators followed clear inclusion/exclusion criteria with dual review for all titles, abstracts, full texts. The summary of our exclusion codes can be found in Appendix B of the report.
Peer Reviewer #5	Methods	I find it puzzling that Pubmed was not used as a source to identify studies to consider. A number of studies that are promising with regard to development of objective diagnostic methods were not listed as included or excluded, thus suggesting they were overlooked. However, the rigorous exclusion criteria would probably have eliminated, most, if not all, of the studies which I have happened to notice were missing from the lists provided. The statistical methods that were used were appropriate for a field far more mature—and well-funded—than ME/CFS. The authors worked hard to evaluate the papers they selected for fulfilling the statistical criteria they outlined.	Thank you for your comments. We did not include any studies of intermediate outcomes such as biomarker studies which may be what you are referring to. Ovid Medline would include studies indexed in PubMed.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #6	Methods	Given the current state of ME/CFS research I do not believe the inclusion and exclusion criteria to be justifiable. The vast majority of ME/CFS research is excluded from the report. The limited number of studies included are for the most part not particularly good. Again, this is at least acknowledged in the report. This begs the question: Is the current state of ME/CFS research sufficiently advanced to warrant such a report? A more appropriate use of resources might have been to discover what the greater body of research actually does or does not tell us about ME/CFS, i.e., a focus on problem setting rather than an attempt at problem solving. I do not believe we are yet at the stage of asking the right questions let alone answering them.	Thank you for your comments. One of the purposes of this report is to identify the need for future research. Fully summarizing everything that is known about ME/CFS was beyond the scope of this report.
TEP Reviewer #6	Methods	Diagnostic criteria and definitions for outcome measures are not clearly articulated. A range of outcome measures are used in the studies reviewed but there is no real discussion of how appropriate they might be for use with the target population, e.g., are all self-report measures of physical function equally valid across all conditions.	Thank you for this comment. We have expanded our discussion regarding appropriateness of outcome measures used as well as provided a review of these measures and whether they are validated or not in Appendix J of the report.
TEP Reviewer #6	Methods	Statistical methods are only as useful as the data being analyzed.	We agree.
Public Reviewer # 49	Methods	What about the proteomics study showing abnormal proteins in CSF of patients with ME? Did you review that one? http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0017287	This study has been reviewed, and does not contain evidence that would meet our inclusion criteria for this review. We included any biomarker studies aimed at diagnosing the syndrome of ME/CFS, had a comparator group, and reported on measures of diagnostic validity, accuracy, or concordance.

Commentator & Affiliation	Section	Comment	Response
James H. Mills	Methods	<p>The evidence review stated regarding the Oxford definition that “we elected to include trials using any predefined case definition but recognize that some of the earlier criteria, in particular the Oxford (Sharpe, 1991) criteria, could include patients with 6 months of unexplained fatigue and no other features of ME/CFS. This has the potential of inappropriately including patients that would not otherwise be diagnosed with ME/CFS and may provide misleading results.” (Chapter 4, page 77)</p> <p>This is bad science. The authors must recognize that this will produce misleading results. It is not scientifically valid to compare treatments across these eight (8) case definitions. By doing so, the assessment of treatments is flawed.</p>	<p>We appreciate that the case definitions are very different and that some are more inclusive than others and may reflect less severe cases or non-cases of ME/CFS as is outlined in the Key Question 1 results in the report. After consultation with our key informants and technical expert panel, we did elect to include all case definitions in the report a priori for several reasons. first of all, there are very little trials and excluding some of these definitions would limit the evidence even further than is already outlined. secondly, the intent was that this could at least provide a foundation to determine what interventions may be effective. Where available, we compared findings using different case definitions to determine if findings were consistent or not across studies. We have expanded the discussion of our future research needs to include that future studies should perform sensitivity analysis to determine differences between case definitions as well as subgroups of patients that meet different criteria. We have elected to use the term ME/CFS at the outset of the report in order to not risk missing important and/or informative evidence that may be labeled under one term or another. By using these terms synonymously throughout the report, we are not endorsing or refuting that these labels reflect the same disease state. We are hopeful that the evidence reported under Key Question 1 will help to shed light on this controversial topic for the P2P workshop.</p>

Commentator & Affiliation	Section	Comment	Response
James H. Mills	Methods	<p>The evidence review stated regarding the Oxford definition that “we elected to include trials using any predefined case definition but recognize that some of the earlier criteria, in particular the Oxford (Sharpe, 1991) criteria, could include patients with 6 months of unexplained fatigue and no other features of ME/CFS. This has the potential of inappropriately including patients that would not otherwise be diagnosed with ME/CFS and may provide misleading results.” (Chapter 4, page 77)</p> <p>This is bad science. The authors must recognize that this will produce misleading results. It is not scientifically valid to compare treatments across these eight (8) case definitions. By doing so, the assessment of treatments is flawed.</p>	<p>(continued)</p> <p>We have edited our report to highlight any differences noted when different case definitions are used; it was our intent to err on the side of including important and/or informative evidence from earlier studies and to also highlight differences if differences exist.</p>
James H. Mills	Methods	<p>Regarding the “limitations of the evidence” the report states “Given the breadth of symptoms in ME/CFS, we a priori elected to not review symptom related outcomes except for fatigue. Some interventions may have revealed benefit for other characteristics of ME/CFS and this review would not have identified these outcomes.” (Chapter 4, page 78)</p> <p>This approach does not give a complete picture of the disease. As previously mentioned, post exertional malaise (PEM) should also have been considered. As drafted, the evidence review is incomplete. It does not give the P2P panel members the necessary background and foundation for the recommendations that they are being asked to make.</p>	<p>Although we recognize the importance of better understanding PEM, the diagnoses and treatment of individual symptoms of ME/CFS was beyond the scope of this report. Other experts will be speaking to these topics at the P2P workshop.</p> <p>The advice of the Technical Expert Panel was that it would be most meaningful and helpful to focus on the syndrome of ME/CFS and the universally experienced symptom of fatigue. We identify areas for future research, including a systematic review on PEM diagnosis and treatment, which would be a topic unto itself.</p>
James H. Mills	Methods	<p>The P2P panel must be made aware of all relevant research. The inclusion/exclusion choices will determine what evidence is considered and, thus, what conclusions are drawn. The fact that over 90% of the 914 articles reviewed were excluded certainly indicates that the inclusion and exclusion criteria were quite restrictive.</p>	<p>Thank you for your comments. We only included studies that directly answered our Key Questions. Other invited guests will be informing the P2P working group on topics outside of the scope of this review.</p>

Commentator & Affiliation	Section	Comment	Response
Sister Sandra Duma, OSF, MS Ed	Methods	<p>...2) The acceptance of 8 disparate ME or CFS definitions as equivalent in spite of dramatic differences in inclusion and exclusion criteria</p> <p>3) The bad science reflected in citing Oxford's flaws and then using Oxford studies anyway</p>	<p>Although we recognize the importance of better understanding PEM, the diagnoses and treatment of individual symptoms of ME/CFS was beyond the scope of this report. Other experts will be speaking to these topics at the P2P workshop.</p> <p>The advice of the Technical Expert Panel was that it would be most meaningful and helpful to focus on the syndrome of ME/CFS and the universally experienced symptom of fatigue. We identify areas for future research, including a systematic review on PEM diagnosis and treatment which would be a topic unto itself.</p>
Sister Sandra Duma, OSF, MS Ed	Methods	<p>...5) The flawed process that used non-experts on such a controversial and conflicted area</p> <p>6) Flawed search methods that focused on fatigue</p> <p>7) Poorly designed and imprecise review questions</p> <p>8) Misinterpretation of cited literature.</p>	<p>Thank you for your comments – the review investigators are experts in performing systematic reviews following scientific methodology. This expertise is critical to any research project. Content expertise, in this case ME/CFS, is also important and we have had an expert in MECFS as part of our research team throughout the process to help inform and guide the team.</p> <p>In addition, the review questions were vetted through the Working Group, a Technical Expert Panel including patients, as well as through AHRQ. We elected a priori, in consultation with the Working Group in the topic refinement phase as well as a Technical Expert Panel during the systematic review phase, to include fatigue as a search term in order to be comprehensive, knowing that many of the papers would not be related to ME/CFS but with the goal of not missing important evidence.</p>

Commentator & Affiliation	Section	Comment	Response
Charmain Proskauer	Methods	<p>I have three comments, two regarding the ratings given to evidence for the effectiveness of CBT and Graded Exercise Therapy in the draft report. I feel strongly that these ratings should be re-evaluated, and downgraded in the final version of the report. The other comment is about important work omitted in the reporting of harms.</p> <p>Note: I suspect that the pre-established, pre-determined “objective criteria” used for these reports will preclude any corrections based on what is actually known about the condition of ME/CFS, but I hope that this is not true. If we present what little that has been scientifically studied as “what is known”, this will lead to a very skewed and misleading perception about this very serious illness.</p>	<p>Thank you for your comments. We have followed methodological standards in rating the quality of the individual studies and the rating the strength of the body of evidence. We have expanded our discussion of limitations of these trials.</p>
Christopher Heppner, PhD	Methods	<p>I offer here a few comments on the recently released preliminary draft of the AHRQ report on Diagnosis and Treatment of Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS). First, I want to point to the intellectual absurdity of first admitting that ME and CFS may well describe different populations, and that definitions that do not make PEM mandatory may exacerbate this problem. And yet the authors go ahead and include all definitions on the same level. They then list their Key Questions that intentionally omit all reference to attempts to understand the underlying processes of this disease/these diseases. They are interested only in Diagnosis and Treatment. But how can one arrive at an accurate Diagnosis without some understanding of the disease(s) being diagnosed? They set out to answer a question already made unanswerable before they begin. The whole project is premature and doomed, as many of us protested to NIH some time ago.</p>	<p>Although we recognize the importance of better understanding PEM, the diagnoses and treatment of individual symptoms of ME/CFS was beyond the scope of this report. Other experts will be speaking to these topics at the P2P workshop.</p> <p>The advice of the Technical Expert Panel was that it would be most meaningful and helpful to focus on the syndrome of ME/CFS and the universally experienced symptom of fatigue. We identify areas of future research, including a systematic review on PEM diagnosis and treatment, which would be a topic unto itself.</p> <p>We have expanded our discussion of the limitations, and applicability and future research sections to highlight the need for subgroup analysis to determine how different populations may respond.</p> <p>The scope of this report was not to review etiology but rather to help inform on aspects of diagnosis and treatment of the condition ME/CFS.</p> <p>Although we recognize the importance of better understanding PEM, the diagnoses and treatment of individual symptoms of ME/CFS was beyond the scope of this report. Other experts will be speaking to these topics at the P2P workshop.</p>

Commentator & Affiliation	Section	Comment	Response
Christopher Heppner, PhD	Methods	<p>In the previously published “Background and Objectives for the Systematic Review” the authors report that “when patients were surveyed in April 2013 as part of the US Food and Drug Administration’s (FDA’s) patient-focused drug development initiative, treatments were divided into two broad categories, those intended to treat the underlying cause of the disease and those targeting specific symptoms. The first category included immune modulators such as rintatolimod (a.k.a. Ampligen) and rituximab, and antiviral and antibiotic medications.” Quite so—a proper distinction to make. They also state that “This report focuses on the clinical outcomes surrounding the attributes of fatigue, especially post-exertional malaise and persistent fatigue...because these are unifying features of ME/CFS that impact patients.” Again, quite proper—I like that word “unifying.” But what happened between those brave words and the completed Draft Report? That “unifying” has been withered to an “and/or,” so that definitions like the Oxford that do not include PEM, and qualify “fatigue” as simply a “subjective sensation” are allowed equal status with the CCC and ICC which do demand PEM as an essential symptom. That little word “or” makes a world of difference. These changes make me wonder if there was rethinking or outside influence between the initial statement and the now published Draft. Whatever the case, the shift has been disastrous. It is accompanied by a list of reasons for “Inclusions” and “Exclusions” that prefaces the lamentably short list of “Included Studies” and the interminable list of “Excluded Studies,” which, in spite of brave statements about the inclusion of unpublished and other “grey” area texts, still excludes many important published and unpublished documents. Those “Excluded” studies include key studies by VanNess, Snell and Stevens, and more recently by others that established the fact that a two-day VO2 Max test will, on the second test, show a marked fall in performance among ME patients that clearly demarcates them from others who also suffer from fatigue. This fact won’t go away, but it can be “disappeared,” and it seems it has been “disappeared” from this report, under Exclusion codes 9 and 3. Another good study, from Julia Newton’s Newcastle group, confirms the centrality of PEM from another angle—Jones D.E., et al, “Loss of capacity to recover from acidosis on repeat exercise in chronic fatigue syndrome: a case-control study.” It concludes that “when exercising to comparable levels to normal controls, CFS patients exhibit profound abnormality in bioenergetic function and response to it. Although exercise intervention is the logical treatment for patients showing acidosis, any trial must exclude subjects who do not initiate exercise as they will not benefit.”</p> <p>This study is excluded under Exclusion Code 8, “Wrong study design for a Key Question.” But the study in fact does contribute to the diagnostic toolkit that a physician could use, in my view. It also adds to the evidence for the centrality of PEM as a diagnostic criterion; all such studies seem to have been deselected or degraded in one way or another, whether by design or by coincidence is not clear.</p>	<p>Thank you for your comments. There have been no outside influences in our systematic review and we have operated independently.</p> <p>Although we recognize the importance of better understanding PEM, the diagnoses and treatment of individual symptoms of ME/CFS was beyond the scope of this review. Other experts will be speaking to these topics at the P2P workshop.</p> <p>We appreciate that the case definitions are very different and that some are more inclusive than others and may reflect less severe cases or non-cases of ME/CFS as is outlined in the Key Question 1 results in the report. After consultation with the Working Group and Technical Expert Panel, we did elect to include all case definitions in the report a priori for several reasons. First, there are very few trials and excluding some of these definitions would limit the evidence even further than is already outlined. Second, the intent was that this could at least provide a foundation to determine what interventions may be effective. Where available, we compared findings using different case definitions to determine if findings were consistent or not across studies. We have expanded the future research needs discussion to indicate that future studies should perform sensitivity analysis to determine differences between case definitions as well as subgroups of patients that meet different criteria.</p>

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Commentator & Affiliation	Section	Comment	Response
Christopher Heppner, PhD	Methods	<p>In the previously published “Background and Objectives for the Systematic Review” the authors report that “when patients were surveyed in April 2013 as part of the US Food and Drug Administration’s (FDA’s) patient-focused drug development initiative, treatments were divided into two broad categories, those intended to treat the underlying cause of the disease and those targeting specific symptoms. The first category included immune modulators such as rintatolimod (a.k.a. Ampligen) and rituximab, and antiviral and antibiotic medications.” Quite so—a proper distinction to make. They also state that “This report focuses on the clinical outcomes surrounding the attributes of fatigue, especially post-exertional malaise and persistent fatigue...because these are unifying features of ME/CFS that impact patients.” Again, quite proper—I like that word “unifying.” But what happened between those brave words and the completed Draft Report? That “unifying” has been withered to an “and/or,” so that definitions like the Oxford that do not include PEM, and qualify “fatigue” as simply a “subjective sensation” are allowed equal status with the CCC and ICC which do demand PEM as an essential symptom. That little word “or” makes a world of difference. These changes make me wonder if there was rethinking or outside influence between the initial statement and the now published Draft. Whatever the case, the shift has been disastrous. It is accompanied by a list of reasons for “Inclusions” and “Exclusions” that prefaces the lamentably short list of “Included Studies” and the interminable list of “Excluded Studies,” which, in spite of brave statements about the inclusion of unpublished and other “grey” area texts, still excludes many important published and unpublished documents. Those “Excluded” studies include key studies by VanNess, Snell and Stevens, and more recently by others that established the fact that a two-day VO₂ Max test will, on the second test, show a marked fall in performance among ME patients that clearly demarcates them from others who also suffer from fatigue. This fact won’t go away, but it can be “disappeared,” and it seems it has been “disappeared” from this report, under Exclusion codes 9 and 3. Another good study, from Julia Newton’s Newcastle group, confirms the centrality of PEM from another angle—Jones D.E., et al, “Loss of capacity to recover from acidosis on repeat exercise in chronic fatigue syndrome: a case-control study.” It concludes that “when exercising to comparable levels to normal controls, CFS patients exhibit profound abnormality in bioenergetic function and response to it. Although exercise intervention is the logical treatment for patients showing acidosis, any trial must exclude subjects who do not initiate exercise as they will not benefit.”</p> <p>This study is excluded under Exclusion Code 8, “Wrong study design for a Key Question.” But the study in fact does contribute to the diagnostic toolkit that a physician could use, in my view. It also adds to the evidence for the centrality of PEM as a diagnostic criterion; all such studies seem to have been deselected or degraded in one way or another, whether by design or by coincidence is not clear.</p>	<p>(continued) The advice of the Technical Expert Panel was that it would be most meaningful and helpful to focus on the syndrome of ME/CFS and the universally experienced symptom of fatigue. We have identified areas of future research, including a systematic review on PEM diagnosis and treatment, which would be a topic unto itself.</p>

Source: <http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2004>
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Christopher Heppner, PhD	Methods	<p>There is more. Cort Johnson in his latest piece on his website healthrising.com has dug out many important studies that were not even included in the “Excluded” category, but somehow completely overlooked—or passed by? Quite a few were, ironically, funded by NIH. They include four of the Lights’ gene expression studies, and Julia Newton’s important study of interaction between the ANS and peripheral muscle tissue under exercise. In fact, looking at this pattern, it seems almost as if a deliberate decision was made at some level to avoid or discard all studies that showed explicitly atypical biological responses to exercise in ME/CFS patients.</p> <p>Such disturbed responses have now been made clear in numbers charted for exercise tests, and made graphically clear in gene and cytokine responses. They have objective, visible existence.</p>	<p>As stated above, the intent of this report was not to review the etiology of ME/CFS or of individual symptoms that a patient experiences.</p>

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Christopher Heppner, PhD	Methods	<p>Science proceeds by formulating falsifiable hypotheses, which upon testing are either confirmed, altered, or falsified. The Oxford definition, which has been accepted on an equal footing with more recent, and better, definitions for this review, makes “fatigue” the “principle” and only required “symptom” for CFS. But this innocent looking word “symptom” has a very specific meaning within this definitio, and I shall quote verbatim from the Oxford definition to emphasize my point here:</p> <p>“When used to describe a symptom this is a subjective sensation and has a number of synonyms including, tiredness and weariness. ... The symptom of fatigue should not be confused with impairment of performance as measured by physiological or psychological testing. The physiological definition of fatigue is of a failure to sustain muscle force or power output.”</p> <p>The wording is careful—though I disagree profoundly, the writers were not stupid or inarticulate—and I believe they meant and considered what they wrote. It is clear now that they were simply wrong in their definition of “fatigue” in ME/CFS, and that we now have many studies from different sources using different approaches that definitively falsify this hypothesis. There are measured tests of “impairment of performance”, whether we look at what happens when patients perform moderate exercise, or the highly stressful two day VO2Max test, which cannot be fudged. Since “fatigue” as “subjective sensation” is the central “symptom” of CFS in the Oxford definition, that definition has been falsified, and can no longer be legitimately used in research; studies that have used it must either be discarded, or placed in a separate category. To continue including them on a par with studies done under later and better (though still imperfect) definitions is to render the task of arriving at a better definition impossible. And that is what has happened here; there is no real answer to Key Question 1, and the decision to include all studies done under any definition on an equal basis made that impossible from the start, as indeed the opening discussion suggests as likely. This whole AHRQ exercise should be “Excluded” on the grounds they list as “8 Wrong study design for Key Question.”</p>	<p>We appreciate that the case definitions are very different and that some are more inclusive than others and may reflect less severe cases or non-cases of ME/CFS as is fully outlined in the Key Question 1 response of the report. After consultation with the Working Group and Technical Expert Panel, we did elect to include all case definitions in the report a priori for several reasons. First of all, there are very few trials and excluding some of these definitions would limit the evidence even further than is already outlined. Secondly, the intent was that this could at least provide a foundation to determine what interventions may be effective. Where available, we compared findings using different case definitions to determine if findings were consistent or not across studies. We have expanded the discussion of our future research needs to include that future studies should perform sensitivity analysis to determine differences between case definitions as well as subgroups of patients that meet different criteria. Fatigue was chosen as a symptom to include as it was universal to all case definitions.</p>

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Christopher Heppner, PhD	Methods	<p>The listings in this “Key” to these codes leads one to some serious absurdities, as in the case of the Mella and Fluge trial of Rituximab which was “Excluded” under Code 12, “Inadequate duration.” This is sheer relevance/absurdity—what counts is the effectiveness of an intervention, not how long it is applied before producing an effect; the application of this test elsewhere in medicine would exclude emergency heart surgery, joint replacement, a session of chemo for cancer, etc. etc. In fact, it took several months for the Rituximab infusion to produce results, and patients were followed for a long time, so that an intelligent understanding of the intervention would not have “disappeared” this trial at all. This little trial, very small as it admittedly was, has had a considerable effect on researchers in the field, focusing their attention on the probability that there is at the least an autoimmune (or autoinflammatory) component to ME, which aligns it further with MS. The authors’ comment that the synchronous improvement in all fields points to their having touched on a “central mechanism for the symptom maintenance” by depleting B cells should be taken very seriously as indicating a path to future research. Oddly enough, the authors of the Draft do assume that ME/CFS is a “relapsing and remitting” disease, which is part of their reason for demanding a certain length in a trial—but would they have used that phrase if the Mella and Fluge trial had never taken place? I doubt it. One can also fear that there is literal prejudice at work in the imposition of a minimal duration of intervention—medical interventions can be of very short duration, but behavioral interventions usually take time to work, and I suspect that there was a prejudgement that any really acceptable intervention would belong to the latter group—CBT or GET, in other words. Be that the case or not, it is fact that most of the purely “medical” interventions that have resulted in clear gains for at least some of the participants have been excluded, “disappeared,” under one code or another.</p>	<p>We performed secondary searches to identify trials of other medications that typically would be given for a duration of <12 weeks, but had outcome data extending 12 weeks or longer. As a result the Fluge trial and an additional trial of acyclovir have been added to the discussion of medication interventions.</p>

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Christopher Heppner, PhD	Methods	<p>Back to another but related point. The earlier statement of intent cited above included the differentiation of intended outcomes for trials into “disease modifiers” and “symptom” modifiers. The Rituximab trial was one of rather few “disease modifiers”; others included the Ampligen (Rintatilomod) and the antiviral trials headed by Lerner, who has several papers. But most of Lerner’s papers are “disappeared” by Exclusion Codes; one is a Code 3–“does not address a Key Question.” This 2012 paper concludes that a very high % of a subset of ME patients manifest “a prolonged elevated antibody level against the encoded proteins EBVduTPase and EBV DNA polymerase,” suggesting quite strongly that these may constitute a subset of CFS patients. Why is the diagnosis of a possibly/probably definable subset within the overall disease not a valuable addition to the diagnostic toolkit for ME/CFS? An earlier Lerner paper from 2002 concluded that “16 CFS patients ...with EBV-persistent infection (EBV singlevirus subset) are improved after 6 months of continuous pharmacokinetic dosing with valacyclovir. Nine CFS patients with EBV/human cytomegalovirus co-infection did not benefit from 6 months of similar treatment.” This is “disappeared” under Exclusion Code 7, “wrong outcomes.” Putting aside the general question of what “wrong outcomes” might possibly mean, in what way is this such an outcome? It supports the later suggestion that there is probably a subset of ME/CFS patients with persistent EBV infection who appear to improve with antiviral treatment. Is this not potentially very useful information for both diagnosis and treatment? Are there subsets visible within the ME/CFS community? It seems very possible, and these essays, and others showing the prevalence of ME/CFS after adolescent EBV mono also suggests that there are and that this is one of them. Why suppress this?</p>	<p>We included studies that reported on outcomes of diagnostic accuracy or concordance. Many biomarker studies are early studies looking for associations but are not yet studied as a diagnostic tests.</p> <p>In key question two, several studies enrolled specific subsets of patients with symptoms and testing suggestive of viral involvement and this was highlighted in this section. The energy index outcome was not considered one of the included outcomes.</p> <p>This study (Lerner, 2002) should be excluded because there is no intervention comparison group (the “control group” also got the drug; the comparison was between two groups: single-virus EBV infections vs EBV/human cytomegalovirus co-infections).</p>

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Christopher Heppner, PhD	Methods	<p>I will pass over the treatment of the PACE trial quickly because many have doubtless commented on the fact that despite claims to have looked at much out-of-the-way material, the team seems to have missed the important facts that besides being based on the Oxford definition, which includes depression and denies that CFS patients have more than a “subjective sensation” of fatigue—in spite of extensive research showing its very real existence—this trial claimed as “recovered” patients who still filled the requirement for entry. The authors have also gone to court to defend their refusal to release the original data of the trial, though such release is increasingly regarded as necessary for full validity. Despite all this, the PACE gets a moderate approval, though there is an overall reminder that all the trials considered for this review have some basic weaknesses.</p>	<p>We agree that there are some limitations to the PACE trial and have expanded our discussion of this throughout the report, including updating the information about recovery and harms in light of recent publications. Our intention at the outset of this report was to be as inclusive as possible to try to get all available data. We appreciate that there are limitations to the EBM approach in some circumstances. Our goal was to review what evidence is available and to inform the P2P about limitations, applicability and focus for future research. Reflective of the purpose of the P2P workshop, one of the goals of this review was to highlight the gaps in the current research and provide recommendations for future research. The practices and policies of the NIH are outside of our control.</p>

Commentator & Affiliation	Section	Comment	Response
Christopher Heppner, PhD	Methods	<p>(continued) I could go on, but will finish with a few comments on the use of EBM methodology in this case. Nigel T. James published a letter in BMJ Clinical Research (Aug 1996), close to the formal inauguration of EBM as a defined movement, from which I shall quote one paragraph: "Evidence based medicine seems to avoid all contact with first hand evidence by replacing original findings with subjectively selected, arbitrarily summarised, laundered, and biased conclusions of indeterminate validity or completeness. It has been carried out by people of unknown ability, experience and skills using methods whose opacity prevents assessment of the original data." This is a rather irascible, intemperate response, but not without some application to the review discussed here. There is no question that the EBM movement has had many successes, mostly in fields where there is a large body of published research on a defined intervention used in a clearly defined condition. It has improved treatment for some conditions, and has saved lives as a result. But there is also the growing feeling in some recent work, that critiques EBM and proposes new models such as "narrative reviews," that EBM is running into serious problems, including the overwhelming of new lines of research by old and established criteria—remember that it took one doctor 20 years to overthrow the established model of how stomach ulcers are caused, 20 years and 3 inflections of a bacteria infection upon himself. I fear that something like that is happening here. New lines of thought and research are buried or "disappeared" under the weight of studies done largely under definitions that I have argued above have now been thoroughly falsified; EBM can represent the dead hand of the past strangling the birth of the new and more accurate.</p>	<p>We agree that there are some limitations to the PACE trial and have expanded our discussion of this throughout the report, including updating the information about recovery and harms in light of recent publications. Our intention at the outset of this report was to be as inclusive as possible to try to get all available data We appreciate that there are limitations to the EBM approach in some circumstances. Our goal was to review what evidence is available and to inform the P2P about limitations, applicability and focus for future research. Reflective of the purpose of the P2P workshop, one of the goals of this review was to highlight the gaps in the current research and provide recommendations for future research. The practices and policies of the NIH are outside of our control.</p>

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Christopher Heppner, PhD	Methods	<p>(continued) The NIH seems to have declared war on the ME/CFS community—researchers, patients and advocates together—in rebuffing their protests and suggestions for better lines of action, and imposing their own models, that throw much of the work onto the shoulders of people who know nothing or very little about the condition. The declaration of war was always shrouded in seemingly friendly words, but the intent was made clear enough through action—the heavy weight of bureaucratic power was constantly present, refusing real input, spending money on the IOM and AHRQ while refusing it to Ian Lipkin, etc. With the publication of this Draft (it may be revised a little, but I foresee no major shifts) the gloves seem to be off. One fears that the moment of a “final solution” may be at hand, and I have no idea what that may lead to. WellPoint has already declared that they will no longer pay for autonomic nervous system testing in ME/CFS, despite all the recent research showing that it is indeed a central player in the condition. What else may follow? I have no idea. I dread what may happen if and when this AHRQ document is given into the hands of a “jury” that explicitly excludes those who know something. Advances in understanding and treating this debilitating and costly—to both patients and society—condition will not come from the NIH under its present mode of operating. I am sorry that your group has lent itself to use in this way and has produced such an unhelpful report, though that was inherent in the request itself. Your energies and experience could doubtless have been better employed in other areas.</p>	<p>We agree that there are some limitations to the PACE trial and have expanded our discussion of this throughout the report, including updating the information about recovery and harms in light of recent publications. Our intention at the outset of this report was to be as inclusive as possible to try to get all available data We appreciate that there are limitations to the EBM approach in some circumstances. Our goal was to review what evidence is available and to inform the P2P about limitations, applicability and focus for future research. Reflective of the purpose of the P2P workshop, one of the goals of this review was to highlight the gaps in the current research and provide recommendations for future research. The practices and policies of the NIH are outside of our control.</p>

Commentator & Affiliation	Section	Comment	Response
Tom Kindlon Assistant Chairperson of the Irish ME/CFS Association	Methods	<p>The Work and Social Adjustment Scale is not valid as an employment measure (or work impairment) and should not be used given actual employment data was reported for some studies.</p> <p>Here are the questions that make up the Work and Social Adjustment Scale Mundt JC1, Marks IM, Shear MK, Greist JH. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. Br J Psychiatry. 2002 May;180:461-4. http://bjp.rcpsych.org/content/180/5/461.long Work and Social Adjustment Scale</p> <p>Rate each of the following questions on a 0 to 8 scale: 0 indicates no impairment at all and 8 indicates very severe impairment.</p> <ol style="list-style-type: none"> 1. Because of my [disorder], my ability to work is impaired. 0 means not at all impaired and 8 means very severely impaired to the point I can't work. 2. Because of my [disorder], my home management (cleaning, tidying, shopping, cooking, looking after home or children, paying bills) is impaired. 0 means not at all impaired and 8 means very severely impaired. 3. Because of my [disorder], my social leisure activities (with other people, such as parties, bars, clubs, outings, visits, dating, home entertainment) are impaired. 0 means not at all impaired and 8 means very severely impaired. 4. Because of my [disorder], my private leisure activities (done alone, such as reading, gardening, collecting, sewing, walking alone) are impaired. 0 means not at all impaired and 8 means very severely impaired. 5. Because of my [disorder], my ability to form and maintain close relationships with others, including those I live with, is impaired. 0 means not at all impaired and 8 means very severely impaired. <p>Comment: Only one of these directly relates to work. This means that scores and in particular changes in scores during a trial (or between treatments) may have nothing to do with changes in employment.</p>	Thank you for your comment. Although the work and social adjustment scale reflects more social adjustment than employment parameters, it has been recognized as one tool to use in measuring meaningful change in patients with ME/CFS.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #50	Methods	<p>Selection of Included Studies and Problems of Exclusion</p> <p>A research review like this one is best applied to a field that has been well analyzed in a large number of research studies. It is a poor fit with ME/CFS. The dismal lack of funding for ME/CFS research has forced researchers to design cheaper, smaller, more limited (in time and in scope) studies intended largely as pilot studies for further inquiry. These studies are frequently published in smaller journals that were not indexed for this review. At this point, researchers are still casting a wide net to figure out what's going on with the ME/CFS disease process. There have been promising studies in fields as disparate as autoimmunity, neuroinflammation, cytokine levels, mitochondrial dysfunction, viral activation, and immune dysfunction, but at this point, no consensus answers have emerged.</p> <p>Because this AHRQ review process was a poor fit with the state of ME/CFS research, the Draft Report's strict inclusion standards essentially edit out the entire field of ME/CFS research. Of the 5,902 potentially relevant results in the initial resource search, only approximately one percent of those studies (64) were found to meet the inclusion criteria [ES-8]. Of these, only 36 were interventional trials [v]. Diagnostic efforts related to the search for biomarkers were dismissed out of hand, and research on disease etiology was, bafflingly, dismissed as unimportant to treatment. Trials of immune modulators and antivirals receive barely a mention – perhaps because any study with a treatment intervention of less than 12 weeks was automatically discarded, even though the Draft Report acknowledges that antiviral and antibiotic treatments show some promise for treating ME/CFS and “are traditionally prescribed for a shorter duration” [ES-30]. These exclusions might be acceptable if the Draft Report simply determined that the state of ME/CFS research does not currently support any clear conclusions about the Report's key questions. Instead, however, the Draft Report departs from this standard of strict inclusion to allow studies based on at least one clearly faulty definition, including one infamous study that has been discredited. The findings from this wrongly defined and poorly designed study are the only results to receive a mention in the Draft Report's conclusions.</p>	<p>The scope of this report was not to review etiology but rather to help inform on aspects of diagnosis and treatment of the syndrome ME/CFS. When biomarker studies reported on diagnostic accuracy or ways of correctly identifying patients with ME/CFS and those without, these studies were reported. We recognize that the biomarker studies may eventually provide insight into the etiology and potentially diagnosis of ME/CFS but its work is still in its infancy for diagnosing the syndrome of ME/CFS and has not been well studied in a way that reports diagnostic validity in patients with diagnostic uncertainty and thus did not meet our inclusion criteria.</p> <p>The purpose of this review is to determine which treatments show benefit or harm rather than to determine the mechanism of how their effect occurs. We recognize that there are several theories pertaining to the mechanisms of action of these interventions and this is beyond the scope of the questions designed by the Planning Committee. The numbers of included studies relative to total number of abstracts reviewed is typical for this type of research, as studies must directly answer our posed research questions, and meet the predefined inclusion criteria. We have repeated the search to look for medication treatments that were appropriately given for 12 weeks to determine if their inclusion would have changed the results. We have added information on a trial of rituximab and a trial on acyclovir to our discussion sections of immune modulators and viral therapies.</p>

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Public Reviewer # 50	Methods	<p>(continued) Research Definitions of ME/CFS</p> <p>At this time, agreeing on an acceptable case definition is one of the central challenges of ME/CFS research, diagnosis, and treatment. Without an adequately specific and widely accepted disease definition, research results may be skewed by inclusion of study subjects outside the actual patient population in question. The Draft Report catalogs eight different existing research definitions of ME/CFS and chooses to treat all of them as essentially equal. That choice dooms the results from the start because a few of the included definitions – in particular the “Oxford definition,” which requires only subjective reports of fatigue without the other standard diagnostic markers of ME/CFS – are drawn so broadly that they pull in patients who may have depression and other causes of fatigue outside the medical condition known as ME/CFS. The Draft Report specifically acknowledges that the Oxford definition “has the potential of inappropriately including patients that would not otherwise be diagnosed with ME/CFS and may provide misleading results” [ES-29, emphasis added]. And then – despite subjecting everything else to inclusion criteria so strict that 99% of studies were discarded – it proceeds to include Oxford-based studies anyway.</p> <p>The PACE Trial</p> <p>The use of Oxford-based studies is particularly significant because it opens the door for the Draft Report to rely upon one particularly poorly designed Oxford-based study known as the PACE trial. The PACE study reported mildly promising results for cognitive behavioral therapy (CBT) and graded exercise therapy (GET) as treatments for ME/CFS. However, those findings are unreliable because of the particularly poor design of the PACE study. First, the study used the Oxford definition, which is likely to accidentally include patients with depressive disorders as a cause of fatigue. In fact, a subsequent paper reported that 46% of the PACE subjects had anxiety, depression, or both. Patients with anxiety and/or depression traditionally respond well to both CBT and GET. In contrast, for actual ME/CFS patients, GET frequently causes additional harms from post-exertional malaise (a point that is included in the Draft Report, to its credit), and the main benefits of CBT are the benefits that therapy provides to any patient suffering a long and disabling illness. Moreover, the PACE authors later admitted that they changed the data requirements just before analysis – patients could enter the study with an SF-36 physical function score of 65 or less, but the authors dropped their standard for “recovery” from a proposed score of 85 to a final score of 60. A patient could enter the study at 65, report a worse post-trial score of 60, and be reported as “recovered.”</p>	<p>(continued)</p> <p>We appreciate that the case definitions are very different and that some are more inclusive than others and may reflect less severe cases or non-cases of ME/CFS as is fully outlined in the Key Question 1 response of the report. After consultation with the Working Group and Technical Expert Panel, we elected to include all case definitions in the report a priori for several reasons. First there are very few trials and excluding some of these definitions would limit the evidence even further than is already outlined. Second, the intent was that this could at least provide a foundation to determine what interventions may be effective. Where available, we compared findings using different case definitions to determine if findings were consistent or not across studies. We have expanded the discussion of future research needs to recommend that future studies should perform sensitivity analysis to determine differences between case definitions as well as subgroups of patients that meet different criteria.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 50	Methods	(continued) With a questionable study population and questionable measures of recovery, there is simply no way that the PACE trial can be trusted as a reliable look at possible treatments for ME/CFS. Because the Draft Report rejected so many other studies for inadequate design, it is mind-boggling that this deeply flawed study would declared one of the Report's few sources of "good" results. In fact, the Draft Report itself warns that results for the CBT and GET studies "need to be interpreted with caution" given flaws in the evaluation of outcomes, over-reliance on self-reporting, and lack of measurement for activity versus inactivity [ES-28]. And then, as with the Oxford definition, the Draft Report goes on to ignore its own cautions and highlight these studies anyway.	(continued) We elected to use the term ME/CFS at the outset of the report in order to ensure we did not miss important and/or informative evidence that may be labeled under one term or another. Given that both terms have been used in the literature (both combined and individually), we have elected to use them together as a single term. We have also attempted to shed light on how the case definitions that are associated with these terms may highlight distinct symptom sets (see key question 1). We are hopeful that the evidence reported under research question one will help to shed light on this controversial topic for the P2P workshop. We have edited our report to highlight any differences noted when different case definitions are used; it was our intent to err on the side of including important and/or informative evidence from earlier studies and to also highlight differences if differences exist. Additionally, we have added language in the introduction, discussion, and future research areas of the report to indicate the desire of the ME/CFS community and patients to adopt the Canadian Carruthers case definition rather than the more non-specific CFS case definitions.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 50	Methods	(refer to previous entries)	<p>(continued) We agree that there are some limitations to the PACE trial and have expanded our discussion of this throughout the report. We have also added additional information on harms and recovery in the PACE trial. We used pre-specified, established criteria to rate the internal validity of the study and this does not apply to the applicability of the study, which we have expanded on in the discussion of the PACE trial.</p> <p>It is our responsibility as independent investigators to strictly report on evidence that is currently available using a pre-defined and structured systematic method. This includes avoidance of literature that does not have a pre-defined comparator group as well as opinion pieces and reviews that are not systematically performed as these have a great risk of being influenced by extraneous factors and incorrectly influencing the interpretation.</p>
Public Reviewer # 51	Methods	<p>Clinical and Research Definitions</p> <p>There is an overall failure to identify what disease is being studied by the P2P panel. In the AHRQ report, eight case definitions are identified and while the report acknowledges this as an issue, it still goes on to answer the questions about subgroups, diagnostics, treatments and harms for all CFS and ME patients based on studies done using any of these eight definitions. In doing so, the Report ignores its own conclusion regarding the differences in populations tied to multiple case definitions. Basically, it cannot be concluded that the same disease is being studied when you apply all of the 8 criteria. It seems unconscionable that this was allowed to happen in the Report and has significantly influenced the acceptance of some studies (e.g. PACE study using the very problematic Oxford definition) while other reports using more the rigorous and more accepted criteria (ICC, CCC) were excluded.</p>	<p>We have highlighted in the introduction, results, discussion, applicability and future research sections of the report the differences between case definitions and that definitions labeled as ME represent a distinct and more impaired population. We included all studies given the paucity of available data but have reported as available any subgroup analysis of patients meeting different definitions. It is the intent that this report serves not as a final step in understanding this condition but as a foundation to help direct future research.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 51	Methods	<p>It appears that some important studies with major implications for advancing clinical biomarkers and treatment modalities were excluded or omitted from the report. Many of these studies were done by well regarded NIH grant awarded researchers so it is bewildering how this could happen. The short comment period for this draft report precludes most of us from doing a thorough review of the literature and comparison to identify omitted studies, furthermore, the information provided in the report is not sufficient to explain why some studies were excluded. With an overall exclusion rate of 90% it appears that the exclusionary criteria for many of these studies were much too harsh and should be re-evaluated. Some areas of specific concern include:</p> <p>1. The exclusion of biomarker and other research that could aid in objective diagnosis because they were considered by AHRQ to “be intended to address etiology”, which was not within the scope of the P2P questions. It is not clear on the rationale for this. One of the biggest concerns for advancing ME/CFS research and treatment revolves around the understanding of the etiology of the disease and development of biomarkers to aid in diagnosis and to provide targets for treatment. This decision should be re-evaluated.</p>	<p>The scope of this report was not to review etiology but rather to help inform on aspects of diagnosis and treatment of the syndrome ME/CFS. When biomarker studies reported on diagnostic accuracy or ways of correctly identifying patients with ME/CFS and those without, these studies were reported. We recognize that the biomarker studies may eventually provide insight into the etiology and potentially diagnosis of ME/CFS but its work is still in its infancy for diagnosing the syndrome of ME/CFS and has not been well studied in a way that reports diagnostic validity in patients with diagnostic uncertainty and thus did not meet our inclusion criteria.</p>
Public Reviewer # 51	Methods	<p>2. Twenty-five studies were eliminated because they had the wrong study design, which included case control studies, letters to the editor, small sample size and non-comparative studies. It appears that only randomized trials were acceptable in regards to study design. Again, I think it should be noted how poor funding for ME/CFS research impacts the ability to carry out robust randomized trials with large sample sizes. It is not clear why AHRQ did not accept case-control studies for their review in light of the vast number of excluded studies. I recommend that this be reconsidered.</p>	<p>Case control and non-comparative studies have a high risk of bias and could mislead the interpretations of the results. Therefore, these types of studies were excluded from the review.</p>
Public Reviewer # 51	Methods	<p>1. Some studies were eliminated because they failed to do the types of analysis required by the AHRQ. This also seems completely unfair and more effort should be given to further review these studies for their potential inclusion in the discussion. Like previously noted, ME/CFS research funding has been abysmal for 30 years, which means that many of the studies that are completed are done so on very small budgets which limit sample size and complicated analysis. It simply is not fair to put these studies aside and not use them to inform decisions about funding future research.</p>	<p>We included very small sized studies but would have a high risk of presenting inaccurate information by including studies with a high risk of bias. One of the purposes of the P2P workshop is to set a research agenda.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 51	Methods	1. Treatment studies required 12 weeks of treatment to be included in the Review. This decision should be evaluated to take into consideration clinical standards of practice for the particular treatment modalities. For example, a study on rituximab (Fluge O, Bruland O, Risa K, et al. Benefit from B-lymphocyte depletion using the antiCD20 antibody rituximab in chronic fatigue syndrome. A double-blind and placebo-controlled study. PLoS ONE. 2011;6(10):e26358. PMID: 22039471), was excluded because the treatment phase was less than 12 weeks. If one was to look at the recommended administration of rituximab for other FDA approved conditions you would see that the Fluge study followed protocols comparable to these other conditions. Treatment with rituximab over 12 weeks is not standard practice and it could be harmful. Therefore, this study should be included in the review. Similar issues are likely to have affected other medication based studies, such as those studying antiviral medications which are often prescribed for periods of less than 12 weeks. This reason for exclusion should be re-evaluated for medication treatment studies and studies that were eliminated should be re-considered.	We have performed a separate search for medications that would appropriately be given for less than 12 weeks and have included the trial of rituximab in our discussion as well as one trial of acyclovir.
B Cella	Methods	No specificity as to what illness is being studied - it appears many "medically fatiguing illnesses were lumped in the same category as ME/CFS...	We included patients with ME/CFS to answer questions about treatment. For diagnosis, we included studies where the ME/CFS diagnosis was a consideration and other causes had been excluded. Ideally, a good study to evaluate a test or method of diagnosis would include patients with diagnostic uncertainty in order to determine how well the test does in separating out those with the disease and those without the disease. This is more challenging when there is not a universally accepted reference standard and we speak of these limitations in the body of the report.
B Cella	Methods	Recent biological findings published in the literature, including those demonstrating the harms done with exercise to ME/CFS patients were not included. However, the PACE trial, with all its flaws and problems were included and obviously misinterpreted.	We reported on harms found in treatment trials that met the inclusion criteria (randomized and comparator). Biological changes noted in cases of patients with the diagnosis of ME/CFS were outside the scope of this report.

Commentator & Affiliation	Section	Comment	Response
Michelle Strausbaugh	Methods	Having said that, I have strong reservations about this draft report in its current form and endorse all concerns detailed in the Dimmock et. al. comments submitted to you on October 18, 2014, including: • the focus on "persistent fatigue not attributable to a known underlying medical condition" and the a priori decision not to review treatment outcomes except for fatigue, making this an evidence review of medically unexplained fatigue which may or may not include an evidence review of the disease(s) known as ME/CFS with its hallmark symptom of Post-Exertional Malaise (PEM) or Post-Exertional Neuro-immune Exhaustion (PENE)	Although we recognize the importance of better understanding PEM, the diagnoses and treatment of individual symptoms of ME/CFS was beyond the scope of this report. Other experts will be speaking to these topics at the P2P workshop. The advice of the Technical Expert Panel was that it would be most meaningful and helpful to focus on the syndrome of ME/CFS and the universally experienced symptom of fatigue. We recommended areas of future research including a systematic review on PEM diagnosis and treatment which would be a topic unto itself.

Commentator & Affiliation	Section	Comment	Response
Michelle Strausbaugh	Methods	Strong Reservations about:using all eight definitions interchangeably, despite evidence -- and even the Evidence Review's own concerns -- that these eight criteria do not necessarily represent the same group of patients all sharing the same underlying pathology; this was especially problematic with regard to the use of Oxford criteria in exercise and psychological therapies	We appreciate that the case definitions are very different and that some are more inclusive than others and may reflect less severe cases or non-cases of ME/CFS as is fully outlined in the Key Question 1 response of the report. After consultation with the Working Group and Technical Expert Panel, we did elect to include all case definitions in the report a priori for several reasons. First, there are very few trials and excluding some of these definitions would limit the evidence even further than is already outlined. Second, the intent was that this could at least provide a foundation to determine what interventions may be effective. Where available, we compared findings using different case definitions to determine if findings were consistent or not across studies. We have expanded the future needs discussion to indicate that future studies should perform sensitivity analysis to determine differences between case definitions as well as subgroups of patients that meet different criteria. We have elected to use the term ME/CFS at the outset of the report in order to not risk missing important and/or informative evidence that may be labeled under one term or another. By using these terms synonymously throughout the report, we are not endorsing or refuting that these labels reflect the same disease state. We are hopeful that the evidence reported under research question one will help to shed light on this controversial topic for the P2P workshop.

Commentator & Affiliation	Section	Comment	Response
Michelle Strausbaugh	Methods	Strong reservations about: lumping all studies of Cognitive Behavioral Therapy (CBT) together without distinguishing between the two opposite primary treatment approaches to this intervention (or even explaining these approaches to the reader): the "false-illness beliefs" school of thought and the "energy-envelope" school of thought; the first seeks to challenge patients' beliefs about their illness with the intention that patients should decrease their attention to their symptoms, the latter seeks to teach patients to live within the limitations of their illness (the energy envelope) by paying more attention to their symptoms; moreover, this lumping of divergent forms of CBT also fails to acknowledge potential harms of CBT for a patient with an organic illness	We have further described the studies on CBT in the results section, so as to point out the similarities and differences in the approaches. We have conducted a sensitivity analysis of the meta-analysis removing dissimilar approaches and have included a description of this finding in the results.
Michelle Strausbaugh	Methods	Strong Reservations about: the failure to include a review of biomarker evidence including cardiopulmonary exercise testing and some clinical trials based on inappropriate duration criteria that could distinguish subgroups and/or diagnostic criteria as well as call into question the suitability of graded exercise therapy as a potential treatment intervention; Dimmock et. al's comment with regard to biomarker data is worth repeating here to underscore its importance: "Ultimately, patterns of common symptoms are not the solution to the diagnostic challenges of ME. Objective biomarkers are."	The scope of this report was based on the questions designed by the Planning Committee. It was not the intent to review etiology but rather to help inform on aspects of diagnosis and treatment of the syndrome ME/CFS. When biomarker studies reported on diagnostic accuracy or ways of correctly identifying patients with ME/CFS and those without, these studies were reported. We recognize that the biomarker studies may eventually provide insight into the etiology and potentially diagnosis of ME/CFS but its work is still in its infancy for diagnosing the syndrome of ME/CFS and has not been well studied in a way that reports diagnostic validity in patients with diagnostic uncertainty and thus did not meet our inclusion criteria. The purpose of this review is to determine which treatments show benefit or harm rather than to determine the mechanism of how their effect occurs. We recognize that there are several theories pertaining to the mechanisms of action of these interventions and this is beyond the scope of this review and our expertise.

Commentator & Affiliation	Section	Comment	Response
Michelle Strausbaugh	Methods	strong reservations about: a failure to adequately review methodological flaws in the PACE trial which, due to its size, randomization, and comparative interventions design, resulted in the overstatement of the quality of evidence for CBT and GET; while the draft report does acknowledge it had no access to study protocols (though for the PACE trial they are readily available -- see White, et. al "Protocol for the PACE trial" BMC Neurol. 2007 Mar 8; 7:6) which would have allowed for a more thorough examination of outcome and analysis reporting bias, the draft report does not examine problems with the selection criteria, lack of actigraphy data, the anemic level of improvement across ALL interventions (even in the GET arm, patients remained very ill -- outcome measures like SF-36 scores and the 6min walk test demonstrate that ME/ CFS patients remained sicker compared to other diseases like pulmonary or congestive heart disease), post hoc changes to data analysis that theoretically could result in a patient entering the study functionally better than he/she ended it)	We agree that there are some limitations to the PACE trial and have expanded our discussion of this throughout the report. Other studies also contributed to the overall strength of evidence for both CBT and GET outcomes. Additional results from the PACE trial have allowed us to include additional data on harms and the 6-minute walk test.

Commentator & Affiliation	Section	Comment	Response
Michelle Strausbaugh	Methods	<p>Strong reservations about: several a priori decisions on treatment outcomes biased the analysis of treatment studies including the decision to focus on fatigue thereby excluding PEM, the almost exclusive use of self-report measures (which by their very nature are subjective), the lack of physical function outcomes, and the lack of objective outcomes such as actigraphy data; I cannot agree more with the Dimmock et al statement, "the a prior decision to focus on self-report measures and changes in fatigue (as opposed to other ME symptoms) narrowed the scope of the Evidence Review. Including studies that used changes in physiological measures like antibody titers would have broadened the number of interventions examined by the Review." This is particularly vexing given that treatments were examined with the expressed purpose of noting what they might reveal about etiology (while etiological studies were ignored), making it hard not to feel there is inherent bias in favor of behavioral studies</p>	<p>The scope of this report was based on the questions designed by the Planning Committee. It was not the intent to review etiology but rather to help inform on aspects of diagnosis and treatment of the syndrome ME/CFS. When biomarker studies reported on diagnostic accuracy or ways of correctly identifying patients with ME/CFS and those without, these studies were reported. We recognize that the biomarker studies may eventually provide insight into the etiology and potentially diagnosis of ME/CFS but its work is still in its infancy for diagnosing the syndrome of ME/CFS and has not been well studied in a way that reports diagnostic validity in patients with diagnostic uncertainty and thus did not meet our inclusion criteria.</p> <p>The purpose of this review is to determine which treatments show benefit or harm rather than to determine the mechanism of how their effect occurs. We recognize that there are several theories pertaining to the mechanisms of action of these interventions and this is beyond the scope of this review and our expertise.</p>

Commentator & Affiliation	Section	Comment	Response
Michelle Strausbaugh	Methods	as a result of the review protocol established by AHRQ, the draft report fails to address the broader but essential questions of whether ME and CFS are the same disease, if ME is a more severe subset of a larger CFS diagnostic category, or if ME and CFS are separate diseases that should be studied separately; while the authors of the draft report are limited by this a priori assumption in the review protocol (which, in turn, dropped this question from the review protocol due to the lack of data available to answer such a question), this remains a fundamental ontological problem that absolutely must be addressed and should be at the very least explored in greater depth in this draft report regarding how the problem might be addressed by future research beyond a sentence acknowledging this issue as controversial	Given that both terms have been used in the literature (both combined and individually) and continue to be used clinically, we have used ME/CFS as a single term for the purpose of this report. We have also attempted to shed light on how the case definitions that are associated with these terms may reflect distinct symptom sets (see Key Question 1). Additionally, we have added language in the introduction, discussion, and future research areas of the report to indicate the desire of the ME/CFS community and patients to adopt the term ME rather than CFS which is considered too non-specific a term
Michelle Strausbaugh	Methods	To Dimmock et. al.'s very thorough and careful analysis of the flaws of this draft report of the Evidence Review, I would add the following: • with regard to potential methodological difficulties with the PACE trial, I would also note that there was concern expressed that the form of pacing used for the "adaptive pacing" intervention arm of the trial differs substantially from the type of pacing generally in use in the patient community(1) or that the "adaptive pacing" approach involved multiple forms of pacing (a term that itself is not well-defined within the medical community) that led to confusion about what kind of pacing was actually effective (2) (though it could be argued the PACE trial introduced a new combination version of pacing); the study authors stated that since there was no manual available for pacing, they created their own in collaboration with the patient organization Action for ME rather than create one based on what was being used in the research of Jason et al.(1999), Pesek et al. (2000), as well the popular online site CFIDS & Fibromyalgia Self-Help (www.cfidselfhelp.org) which has a self-help course that teaches pacing using the Energy Envelope theory and includes a textbook; given that the study authors were themselves involved in creating the "adaptive pacing" interventional arm despite materials available that were specifically based on the very Energy Envelope theory the PACE authors were ostensibly trying to test in their study, it is possible they may have consciously or unconsciously "underpowered" the comparative intervention	We agree that there are some limitations to the PACE trial and have expanded our discussion of this throughout the report. The concerns about the definition of the adaptive pacing intervention should be addressed to the study authors. Where applicable we have expanded on the adaptive pacing group.

Commentator & Affiliation	Section	Comment	Response
Mary Dimmock	Methods	<p>The fundamental question that needs to be addressed is whether the eight (8) "ME/CFS" case definitions encompass the same disease, a spectrum of diseases, or separate, discrete conditions and diseases.</p> <p>It is essential that the AHRQ evidence review and the P2P agenda consider this fundamental question. The failure to tackle this cornerstone question in both the AHRQ evidence review and the P2P agenda puts the scientific validity of the entire P2P Workshop at risk</p>	<p>The role of the evidence report is to provide the evidence available regarding the different case definitions. As outlined in the report, the various case definitions differ in discrete ways. The P2P working group will be using information from the report as well as from other invited guests to make their decisions regarding this question.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 52	Methods	I feel that the inclusion of the Oxford definition in your review is a fatal flaw that will render your efforts at best meaningless and at worst harmful to those with MECFS.	<p>We appreciate that the case definitions are very different and that some are more inclusive than others and may reflect less severe cases or non-cases of ME/CFS as is fully outlined in the Key Question 1 response of the report. After consultation with the Planning Committee and Technical Expert Panel, we did elect to include all case definitions in the report a priori for several reasons. First of all, there are very few trials and excluding some of these definitions would limit the evidence even further than is already outlined. Secondly, the intent was that this could at least provide a foundation to determine what interventions may be effective. Where available, we compared findings using different case definitions to determine if findings were consistent or not across studies. We have expanded the discussion of our future research needs to include that future studies should perform sensitivity analysis to determine differences between case definitions as well as subgroups of patients that meet different criteria.</p> <p>We have edited our report to highlight any differences noted when different case definitions are used; It was our intent to err on the side of including important and/or informative evidence from earlier studies and to also highlight differences if differences exist</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 1	Methods	<p>The case definitions are not interchangeable. Treating them as such in the review ignores the evidence about differences in patient populations.</p> <p>Selected references from Evidence Review (in italics)</p> <p>p. 1 “Currently diagnosing a patient with ME/CFS relies on the use of a set of clinical criteria (case definitions) to distinguish ME/CFS from other conditions that may also present with fatigue.”</p> <p>Results (Structured Abstract) V -- “Multiple case definitions have been used to define ME/CFS and those that require the symptoms of post-exertional malaise and neurological and autonomic manifestations appear to represent a more severe subset of the broader ME/CFS population” (repeated in similar format in the Executive Summary ES-25 (... appear to represent ‘more involved’) and main report p. 60 (appear to represent ‘more impaired’)</p> <p>ES- 1 and p.1 “For this review, ME and CFS will be used synonymously (ME/CFS) and will include the population(s) studied under either of these terms, recognizing that issues regarding terminology are currently unresolved.” [Underlining added.]</p> <p>ES- 26 Several studies attempted to demonstrate that ME, ME/CFS, and CFS case definitions identify different groups of people. Studies did this by identifying people who met one criteria but not the other. Using this approach, it appears that the case definitions labeled as ME and ME/CFS select a population with more impairment, lower functioning, and higher symptom reporting compared with the case definitions labeled as CFS alone.”</p> <p>Conclusions ES-32: “Multiple case definitions for ME/CFS exist with those that require symptoms of PEM, neurological impairment, and autonomic dysfunction representing a more severe form of the condition.”</p> <p>Discussion: The whole evidence review mixes and matches the definitions of ME and CFS. It identifies eight case definitions, notes that those with the labels ME and ME/CFS define a population that is more severely impaired and then treats them as essentially equivalent, which they are not. This approach was continued in the treatment sections, where treatments used for any of the case definitions were analyzed and results reported. One reason given in the review is to allow a “broad representation of patients.” This is not helpful when we are trying to properly diagnose and treat people with ME. They may need and respond to entirely different treatments.</p> <p>The issues are not just of “terminology” they are at the basis of much of the existing confusion, underlie much of the current discussion and fuel current research.</p>	<p>We appreciate that the case definitions are very different and that some are more inclusive than others and may reflect less severe cases or non-cases of ME/CFS as is fully outlined in the Key Question 1 response of the report. We have expanded our discussion of the limitations, applicability and future research to highlight the need for subgroup analysis to determine how different populations may respond.</p> <p>Additionally, we have edited our report to highlight any differences noted when different case definitions are used; it was our intent to err on the side of including important and/or informative evidence from earlier studies and to also highlight differences if differences exist.</p> <p>We have reviewed the letter to the Honorable Kathleen Sebelius and have made note of its recommendations in our discussion.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 1	Methods	(continued) In the Future Research section, the report suggests that “it would be ideal if future intervention studies consistently used an agreed upon single case definition.” Such an agreed upon definition has been put forward. Approximately 50 researchers and clinicians signed an open letter to then US Secretary of Health and Human Services, the Honorable Kathleen Sebelius. The original letter was dated September 23, 2013 and updated with additional signatures on October 25, 2013.	We appreciate that the case definitions are very different and that some are more inclusive than others and may reflect less severe cases or non-cases of ME/CFS as is fully outlined in the Key Question 1 response of the report. We have expanded our discussion of the limitations, applicability and future research to highlight the need for subgroup analysis to determine how different populations may respond. Additionally, we have edited our report to highlight any differences noted when different case definitions are used; it was our intent to err on the side of including important and/or informative evidence from earlier studies and to also highlight differences if differences exist. We have reviewed the letter to the Honorable Kathleen Sebelius and have made note of its recommendations in our discussion.

Commentator & Affiliation	Section	Comment	Response
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Methods	<p>I'm deeply concerned that the many substantial flaws within this report will create an undue risk of significant harm to patients with ME and that it most likely will hamper, retard and confuse the much needed ME/CFS research for years to come. These issues must be addressed before the Evidence Review is issued in its final form.</p> <p>The failure to differentiate between patients with the symptom of subjective unexplained fatigue on the one hand, and objective immunological, neurological and metabolic dysfunction on the other, calls into question the entire Review and all conclusions made about diagnostic methods, the nature of this disease and its subgroups, the benefits and harms of treatment, and the future directions for research.</p> <p>Accepting eight disparate ME or CFS definitions as equivalent in spite of dramatic differences in inclusion and exclusion criteria - even contradictory/mutually exclusive in some aspects - , the Review draws conclusions on subgroups, diagnostics, treatments and harms for all CFS and ME patients based on studies done in any of these eight definitions. In doing so, the Evidence Review disregards its own concerns, as well as the substantial body of evidence that these definitions do not all represent the same disease and that the ME definitions are associated with distinguishing biological pathologies. It is unscientific, illogical and risky to lump disparate patients together without regard to substantive differences in their underlying conditions.</p>	Thank you for your comments. Please see above. We have expanded our discussion of the limitations, applicability and future research to highlight the need for subgroup analysis to determine how different populations may respond.
Public Reviewer # 2	Methods	<p>The Draft Report states that: "We elected to include trials using any predefined case definition but recognize that some of the earlier criteria, in particular the Oxford (Sharpe, 1991) criteria, could include patients with 6 months of unexplained fatigue and no other features of ME/CFS. This has the potential of inappropriately including patients that would not otherwise be diagnosed with ME/CFS and may provide misleading results."</p> <p>This rather important caveat should be given greater prominence in the overall report and any summary if it is a fundamental problem which could undermine the conclusions of the entire review.</p>	Thank you for this comment. Please see above. We have expanded our discussion of the limitations, applicability, and future research sections accordingly.
Public Reviewer # 1	Methods	<p>Although Dr. Melvin Ramsay described ME in 1986 his definition was updated in 1988 – the cutoff year used for this review.</p> <p>The ME case definition as described by Dr. Melvin Ramsay has not been included as one of the case definitions. The earlier version in 1986 is a general reference. On page 17 (3rd paragraph) Ramsay's name is misspelled as "Ramsey" in the description of one of the studies (Jason et al 2012)</p> <p>Ramsay M: Myalgic Encephalomyelitis and Postviral Fatigue States. 2nd edition. London: Gower Medical Publishing; 1988.</p>	Thank you for this comment. Dr. Ramsey presented symptoms that he identified as part of a syndrome but did not present a set of clinical criteria to meet a case definition.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 1	Methods	<p>The ICC definition is for Myalgic Encephalomyelitis (ME). It is for ME for a reason; because of what is known about ME and its underlying pathophysiological dysfunction.</p> <p>Reference in Review p. 1 “The most recent international consensus report advocates moving away from the term CFS in favor of ME ... and to embrace the two terms as synonymous.”</p> <p>The ICC specifically seeks to distinguish ME from CFS as follows: “Individuals meeting the ICC have myalgic encephalomyelitis and should be removed from the Reeves empirical criteria and the National (NICE) criteria for chronic fatigue syndrome.”</p> <p>The publication of the ICC resulted in comment to the article (van der Meer and Lloyd) which resulted in a follow-up response (Broderick) which included the following statements providing more information about the importance of distinguishing the case definition.</p> <p>“Whether patients with less severe conditions represent a continuum, faulty diagnosis or different disease entities can only be determined by future studies”</p> <p>“When advances in scientific technology are applied to patients who meet the more specific case definition of the ICC for ME, the current urgent need for identifying and confirming specific biopathological mechanisms and biomarkers will be facilitated, and our improved understanding of the pathophysiology can then be directed towards enhancing treatment efficacy.”</p>	Thank you - we have reviewed the ICC and its associated primer and made edits to the report accordingly.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 1	Methods	<p>Reconsider the exclusion of the studies looking at biomarkers, cell function, immunologic, virologic/bacterial hormonal etc. (See also comment eight, which deals with related issue)</p> <p>Reference in Review -- ES -1 “This review is not intended to address the question of etiology nor underlying factors that lead to the onset or perpetuation of ME/CFS but rather to focus on the diagnosis and treatment of this syndrome.”</p> <p>ES-25 “Articles that attempted to define an etiology on the basis of a biochemical marker or a particular physiologic test were not included in this review because the intent of these was to identify an etiology rather than understand how the specific test could distinguish patients that would respond to treatment.” As well, subgroups were not studied as they did not report diagnostic testing outcomes.</p> <p>Discussion -- This is a chicken and egg proposition. Accurate diagnosis and treatment will rely on knowing more about the body’s response to ME/CFS. The review paper outright excludes some very important studies that are pointing to biomarkers as well as to other ways of distinguishing ME/CFS patients by subgroups. These papers are important stepping stones; not only to more precise diagnosis of ME/CFS patients but to appropriate treatment for the subgroups the research has begun to demonstrate.</p> <p>Studies excluded include a large literature showing biologic abnormalities in persons with ME/CFS; a literature that directly links to the case definitions. Studies were excluded if they looked at any outcome other than fatigue i.e. pain, antidepressants, sleep treatment (see also comment eight).</p> <p>One of the very interesting sections of the report starts on p. 74 “Findings in Relationship to What is Already Known.” Much of this section is also found in Key Findings and Strength of Evidence p. ES- 25 and on. This material is of considerable importance in providing a context for the larger picture as well as for future research. The [Findings in Relationship to What is Already known] section explains why the review does not look at the research which the study has determined is “focused at discovering etiologies rather than testing diagnostic strategies in patients.” This includes studies on biomarkers and studies on “cell function, immunologic, virologic/bacterial, hormonal etc” which identified subgroups on the basis of exercise testing, cerebral blood flow as measured by arterial spin labeling, gait kinetics, impaired blood pressure variability/hemodynamic instability, bioenergetics (capacity to recover from acidosis) and many others [references to some of these studies included in the review report.]</p> <p>Other relevant studies were not included because they did not report on “diagnostic testing outcomes, such as ROC/AUC, sensitivity</p>	<p>Thank you. We recognize that the biomarker studies may eventually provide insight into the etiology and potentially diagnosis of ME/CFS. However, review of this literature was outside of the scope of this report.</p>

Commentator & Affiliation	Section	Comment	Response
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Methods	Treatment trials that were shorter than 12 weeks were excluded, even if the treatment duration was therapeutically appropriate. The big exclusion here was the rituximab trial; despite following patients for 12 months, it was excluded because administration of rituximab was not continuous for 12 weeks (even though rituximab is not approved for 12 weeks continuous administration in ANY disease). Many other medication trials were also excluded for not meeting the 12 week mark. Exclusion of these studies may also have biased the Review toward including more behavioral and exercise intervention studies, and fewer medication trials.	We performed a secondary search to determine if treatments that were appropriately given for <12 weeks would have changed the results. We found two additional studies and included them in our discussion of the treatment results.
Mary Dimmock et al	Methods	The attached comments reflect significant concerns with how this Evidence Review has been conducted, the diagnostic, subgroup and treatment conclusions drawn by this report and the risk of undue harm that this report creates for patients with myalgic encephalomyelitis (ME). A final version should not be published until these scientific issues are resolved. Most fundamentally, this Evidence Review is grounded in the flawed assumption that eight CFS and ME definitions all represent the same group of patients that are appropriately studied and treated as a single entity or group of closely related entities. Guided by that assumption, this Evidence Review draws conclusions on subgroups, diagnostics, treatments and harms for all CFS and ME patients based on studies done in any of these eight definitions. In doing so, the Evidence Review disregards its own concerns as well as the substantial body of evidence that these definitions do not all represent the same disease and that the ME definitions are associated with distinguishing biological pathologies. It is unscientific, illogical and creates undue risk of harm to lump disparate patients together without regard to substantive differences in their underlying conditions.	We have highlighted differences between case definitions and that definitions labeled as ME represent a distinct and more impaired population throughout the report. We included all studies with available data as it was our intent to err on the side of including any important and/or informative evidence from earlier studies and to highlight differences if such differences existed. We have reported as available any subgroup analysis of patients meeting different definitions.

Commentator & Affiliation	Section	Comment	Response
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Methods	The bad science reflected in citing Oxford's flaws and then using Oxford studies anyway, as well as recognizing the importance of PEM but failing to consider the implications of Fukuda's and Oxford's failure to require it.	We erred on being more inclusive for the case definitions.

Commentator & Affiliation	Section	Comment	Response
Mary Dimmock et al	Methods	<p>Diagnostic methods were assessed without first establishing a valid reference standard.</p> <p>Critical biomarker and cardiopulmonary studies, some of which are in clinical use today, were ignored because they were judged to be etiological studies or used the wrong statistics, regardless of the importance of the data.</p> <p>Treatment outcomes associated with all symptoms except for fatigue were disregarded, potentially resulting in a slanted view of treatment effectiveness and harm.</p> <p>Treatment trials that were shorter than 12 weeks were excluded, even if the treatment duration was therapeutically appropriate.</p> <p>Counseling and CBT treatment trials were inappropriately pooled without regard for the vast differences in therapeutic intent across these trials.</p> <p>Conclusions about treatment effect and harms failed to consider what is known biologically about ME and patients likely response to the therapies that are being recommended.</p> <p>The Evidence Review states that its findings are applicable to all patients meeting any CFS or ME definition regardless of the case definition used in a particular study.</p>	<p>We have emphasized the limitations in diagnostic studies given that there is lack of a valid reference standard and have expanded our discussion of this for the final report.</p> <p>Reviewing the various theories surrounding etiology and the associated studies in biomarkers and cardiopulmonary studies was beyond the scope of this report. Any of these studies that reported on diagnostic testing were included.</p> <p>A priori, the focus of the outcomes was toward the comprehensive syndrome of ME/CFS rather than individual symptoms.</p> <p>We performed a secondary search to determine if other treatments that were appropriately given for <12 weeks would have changed the results. We added additional studies of rituximab and acyclovir to our discussion of medications.</p> <p>We performed a sensitivity analysis of just the CBT trials, excluding the other types of counseling (i.e., support, relaxation, peer counseling) and have added this to the discussion of these trials.</p> <p>We have expanded our discussion section on the concerns surrounding PEM and exercise as well as on the need for future research with subgroup analysis on patients with these symptoms.</p> <p>We have emphasized throughout the importance of considering the different case definitions and the limitations of the results due to this variability.</p>

Commentator & Affiliation	Section	Comment	Response
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Methods	Treatment outcomes associated with all symptoms except fatigue were disregarded, potentially resulting in a slanted view of treatment effectiveness and harm. This decision excluded Dr. Lerner's antiviral work, as well as entire classes of pain medications, antidepressants, anti-inflammatories, immune modulators, sleep treatments and more. If the treatment study looked at changes in objective measures like cardiac function or viral titers, it was excluded. If the treatment study looked at outcomes for a symptom other than fatigue, it was excluded.	The advice of the Technical Expert Panel was that the most meaningful and helpful place to focus would be on the syndrome of ME/CFS and the universally experienced symptom of fatigue. The treatment of individual symptoms of Me/CFS was beyond the scope of the questions designed by the Planning Committee. Other experts will be speaking to these topics at the PTP workshop.
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Methods	Critical biomarker and cardiopulmonary exercise studies, some of which are in clinical use today, were ignored because they were judged to be intended to address etiology, regardless of the importance of the data. This included most of Dr. Snell's and Dr. Keller's work on two day CPET, Dr. Cook's functional imaging studies, Dr. Gordon Broderick's systems networking studies, Dr. Klimas's and Dr. Fletcher's work on NK cells and immune function, and all of the autonomic tests. None of it was considered. Also, the Review fails to discuss the diagnostic utility of CPET.	We agree that there is important work that is being done in the field which was beyond the scope of this report. There will be other invited guests to the P2P workshop that will be addressing these issues.

Commentator & Affiliation	Section	Comment	Response
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Methods	Regarding treatments, the Review explicitly decided to focus on changes in only one(!) symptom, fatigue, and almost exclusively self-reported subjective measures over objective measures of functional capacity, thereby choosing to ignore the critical component PEM (correctly noted by the Review to be a hallmark characteristic of the disease), as well as all other well documented and studied symptoms such as pain or neurological, endocrine, cardiovascular, immunological, cognitive and muscular abnormalities; most of them objectively measurable/verifiable. Inexplicably reducing a neuroimmune illness such as ME to just one single diffuse symptom that can also be found in a myriad of other illnesses, and that can't even be measured objectively, is unacceptable. Including studies that used changes in physiological measures like antibody titers would have broadened the number of interventions examined by the Review. Examining data on objective measures of physical function like activity would have not only broadened the evidence base, but would have introduced data that call into question the assessment of GET benefits. There is no question that the selection of outcomes measures ultimately changed the Evidence Review's conclusions, and the Review must explicitly acknowledge the detrimental impact of those a priori decisions.	The advice of the Technical Expert Panel was that the most meaningful and helpful place to focus would be on the syndrome of ME/CFS and the universally experienced symptom of fatigue. The treatment of individual symptoms of Me/CFS was beyond the scope of this review. Other experts will be speaking to these topics ant the PTP workshop.
Public Reviewer # 53	Methods	In addition to excluding the best minds for the task, the AHRQ has ignored the critical disciplines: etiology; immune, cardiopulmonary, neural , and autonomic biomarkers; as well as Post Exertional Malaise that is crucial to defining the illness of ME and differentiating between those who have it and those who are fatigued, even chronically, because of any number of other conditions. Without this distinction the AHRQ does not have a precise population for which to compare studies.	Although we recognize the importance of better understanding PEM, the diagnoses and treatment of individual symptoms of ME/CFS was beyond the scope of the questions identified by the planning group for this review. Other experts will be speaking to these topics at the P2P workshop.
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Methods	It is scientifically unreasonable and unethical to make recommendations about diagnostics, treatments and harms in one patient population based on studies done in another patient population. Given the evidence that these definitions do not encompass the same populations, this Review must reassess the validity of its core assumption and the conclusions made on the basis of that assumption.	Thank you for your comment. We agree that there are significant limitations in the current state of evidence surrounding the syndrome of ME/CFS, not the least of which is the lack of a universally agreed upon case definition and the heterogeneity of patient populations. One of the purposes of this report is to shed light on the deficits in the body of literature and to provide potential areas of focus for future research.

Commentator & Affiliation	Section	Comment	Response
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Methods	<p>Flawed search methods. Inclusion/exclusion choices apparently shaped what evidence was considered and what conclusions were drawn, and to my mind reflect a poor understanding of ME/CFS research. Some examples of how the above assumptions and protocol choices negatively impacted this Review include:</p> <p>Evidence about the significant differences in patient populations and in the unreliability and inaccuracy of some of these definitions was ignored and/or dismissed. This includes: Dr. Leonard Jason’s work undermining the Reeves Empirical definition; a study that shows the instability of the Fukuda definition over time in the same patients; studies demonstrating that Fukuda and Reeves encompass different populations; and differences in inclusion and exclusion criteria, especially regarding PEM and psychological disorders.</p> <p>Diagnostic methods were assessed without first establishing a valid reference standard. Since there is no gold reference standard, each definition was allowed to stand as its own reference standard without demonstrating it was a valid reference.</p>	<p>Thank you for your comment. Throughout the report we have emphasized the challenges in this body of literature when a diagnostic test cannot be compared to an acceptable reference standard. We have highlighted these limitations and expanded our discussion of applicability and recommendations for future research. We have reviewed the evidence comparing different case definitions and attempted to highlight these differences.</p>
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Methods	<p>The Review never questioned whether the disease theories underlying these treatments were applicable across all definitions. Yet again the failure to be clear and specific about what disease was being studied muddles the findings. It simply isn’t reasonable comparing treatments like Rituximab/Rituxan or Ampligen (targeting a very specific objectively measurable biological issue) with talk and/or exercise therapies (thought to reverse what is assumed to be the patient’s “false illness beliefs”) by pretending that both types are about aimed at the one and same disease.</p>	<p>Thank you for your comments. The purpose of this review is to determine which treatments show benefit or harm rather than to determine the mechanism of how their effect occurs. We recognize that there are several theories pertaining to the mechanisms of action of these interventions and this is beyond the scope of this review.</p>

Commentator & Affiliation	Section	Comment	Response
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Methods	<p>The issue of harms associated with CBT and Graded Exercise Therapy/GET has not been addressed adequately. Again a problem likely caused by the failure to be clear and specific about what disease was being studied. The Review ignored substantial evidence of harms associated with GET, thereby failing to recognize the evidence of well-known correlations between abnormal physiological responses to exercise (as evidenced by significant, distinct responses to exercise in gene expression and cardiopulmonary measures), Post Exertional Malaise/PEM, and harms following GET. This underplays the serious risk of harm for ME patients who are prescribed exercise, and creates a high risk that the Review will be used to perpetuate the harmful prescription of exercise to ME patients who are physically incapable of exercising without incurring harm. Patients who have an organic disease characterized by neurological, immunological and metabolic impairments would not have a meaningful therapeutic response to CBT (based on hypothetical “false illness beliefs”) and would be at higher risk for harm. The Review must clearly acknowledge the harm done to ME patients when psychological theories and treatments are applied to a disease with demonstrated organic pathologies.</p> <p>To claim that correcting patients’ false illness beliefs could adequately treat multiple sclerosis or hypothyroidism would be malpractice and quackery. Similarly, a disease like ME characterized by multisystem dysfunctions and measurable physiological abnormalities cannot be credibly treated by convincing patients that they erroneously believe those physiological problems to exist. The reverse is also true: patients with the single symptom of chronic fatigue are not likely to respond to treatment with antivirals or immune modulators, in the absence of measurable immune dysfunction.</p>	<p>We have reported on harms of CBT and GET where these outcomes are reported in the trials. We have added references for the PACE trial in particular and added this information to the results. There are few trials that reported harms, but we have discussed in the future research section that monitoring of harms and reporting of harms should be more comprehensive and transparent.</p>
Solve ME/CFS Initiative and Research Advisory Council	Methods	<p>Methods</p> <p>In the Literature Search Strategy on page 4 it is noted that “scientific information packets were requested from drug and device manufacturer who potentially had data on the use of medications or devices for ME or CFS, who had the opportunity to submit data using the portal for submitting scientific information packets on the Effective Health Care Program Web site. Seventeen submissions were received”. However, it is not clear where these 17 submissions are listed, how they were analyzed, included or excluded and whether they provided evidence--based information.</p>	<p>The scientific information packet (SIP) submissions did not meet inclusion criteria. When SIP submissions suggested articles that we excluded upon review, the citations were added to the excluded studies list in the report appendix (which lists all articles reviewed that did not meet inclusion criteria).</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 1	Methods	<p>Report does not even look at symptom related outcomes other than fatigue The a priori decision not to include other outcomes is ill-considered and shows a lack of understanding of the condition.</p> <p>“ES-30 “Given the breadth of symptoms in ME/CFS, we a priori elected to not review symptom related outcomes except for fatigue. Some interventions may have revealed benefit for other characteristics of ME/CFS and this review would not have identified these outcomes.”</p> <p>And yet, ES-31 Future Research “It is particularly important for future studies to report findings according to the cardinal features of ME/CFS such as PEM, neurocognitive status, and autonomic function as treatment choices may differ for subsets of the population”</p> <p>From Discussion of ICC definition of ME “Using ‘fatigue’ as a name of a disease gives it exclusive emphasis and has been the most confusing and misused criterion. No other fatiguing disease has ‘chronic fatigue’ attached to its name – e.g. cancer/chronic fatigue, multiple sclerosis/chronic fatigue – except ME/CFS.”</p>	<p>Thank you for this comment - by excluding symptom-related outcomes, we in no way meant to be inconsiderate of the experience of patients. Addressing all symptoms experienced by patients with ME/CFS was outside the scope of the questions designed by the planning committee. We have identified areas of future research, including a systematic review on PEM diagnosis and treatment, which would be a topic unto itself.</p>
Public Reviewer # 53	Methods	<p>...All of the studies that validated our experiences, corroborated her symptoms, gave us criteria for measurement and the ability to document change, that brought some relief and a basis for looking for improvement over time in this story have been left out of the AHRQ review. Those studies as well as Chia’s delving into “smoldering viruses” and every other study by researchers related to pathogens and post-viral syndromes, possible root causes, and other studies that the current AHRQ have found too small for inclusion are precisely the ones that physicians in general practice need to know about—now, even before the whole nut of ME has been cracked—in order to stop harming and begin helping patients. It is faulty review criteria that excludes this most promising science. It needn’t be the case.</p> <p>As if it is not enough for patients to languish for years and decades without real treatment options, when doctors have been told by the NIH that ME is the same thing as CFS, only treated with CBT and GET, they do not take seriously the constellation of symptoms that reveal that ME can be fatal. ...</p>	<p>Thank you for sharing your experiences. We have heard similar experiences from other individuals as well. When we consider evidence on which to base conclusions, we need to look beyond the experience of individuals and look to studies that compare treatments in a way that minimizes the risk that something impacted change in an individual beyond the effects of the treatment provided. Unfortunately, the research in ME/CFS remains primarily with small pilot studies; interventions such as you are describing have not yet been studied in a way that allowed them to meet our inclusion criteria. That said, individual experience continues to provide a basis for justifying future research that can be performed in a manner in which the results can help inform and direct clinical decision making. We have greatly expanded our discussion of limitations, applicability, and future research needs aided by the comments provided by individuals like you. Thank you again.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2	Methods	<p>“Given the breadth of symptoms in ME/CFS, we a priori elected to not review symptom related outcomes except for fatigue.” (Draft review, es30)</p> <p>A problem with this is the we do not have a reliable measure for ‘fatigue’. Much trouble has been caused by researchers seeming to just assume some fatigue questionnaire reliably captures the symptom most troubling to patients with ME/CFS, even when assessing biopsychosocial interventions specifically intended to alter patient cognitions.</p>	<p>Thank you for this comment - we agree that attempts to measure subjective reports of symptoms in an objective manner present with their own set of challenges; we did find in this body of literature that multiple measures were used. We were unable to pool studies because of this heterogeneity and have discussed the limitations to applicability of the findings on this measure.</p>
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Methods	<p>The failure to examine objective measures of function, combined with the failure to consider treatment studies that used biomarker changes such as viral titers, resulted in the exclusion of many studies. These studies would have changed the Review’s conclusions about the effect of CBT and GET on function, and would have expanded the evidence on medication trials.</p> <p>The choice of inclusion and exclusion criteria made by the Review unreasonably excludes critical evidence on diagnostic methods and subgroups.</p>	<p>We have included measures of function where reported (6 MWT for example) but have not included intermediary measures including biomarker studies unless they reported on measures of diagnostic accuracy.</p>
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Methods	<p>The Review excluded all studies examining biomarkers or physiological tests “because the intent of these was to identify an etiology rather than understand how the specific test could distinguish patients that would respond to treatment.” This choice means that hundreds if not thousands of studies were not considered at all, which had the indisputable effect of narrowing the evidence base monumentally. This limitation and its ramifications for the Review’s conclusions must be expressly acknowledged.</p>	<p>We agree that there is important work being done in the field that was beyond the scope of this report. There will be other invited guests to the P2P workshop that will be addressing these issues.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2		<p>Earlier in the history of the biopsychosocial management of ME/CFS, it was recognised that other more objective outcomes were of importance. A 1990 letter from Wessely et al. recognised that an increase in patient's activity must ultimately be the aim of any treatment [1], while a later Wessely et al. response to an RCT [2] which found CBT to be no more effective at increasing self-reported activity than placebo (this study was given exclusion code 9 in the draft review, despite being a rare biopsychosocial study with a placebo control) stated that "the primary aim of treatment is to restore activity and function" and "if a patient completes the program, he or she must have increased their activity, even if everything else remains unchanged." [3] It was therefore argued that the efficacy of CBT had not truly been tested as the patients "may have attended the sessions, but did not comply with the program".</p> <p>Such claims are now rarely made by those who have developed and promote CBT as an effective treatment for CFS. In 2001 an RCT assessing CBT for CFS was published in the Lancet [4] reporting a positive result for patient's self-reported fatigue and functional impairment. Although not released at the time, the trial also collected actimeter data, which found that in this 'positive' trial CBT did not lead to patients being able to increase their activity levels. This finding was repeated in two further trials [5,6] and then finally the data was released in a 2010 meta-analysis [7], where the results were presented as evidence that CBT is effective even without patients needing to increase their activity levels. This actimeter data has also been excluded from the draft review.</p> <p>Although the PACE trial [8] had listed actimeters as an outcome measure in the trial's identifier, and then purchased and used them at baseline, they were later dropped as an outcome measure. [9] In his response to concerns about the lack of objective outcome measures, Professor White stated "We have used several objective outcome measures; the six minute walking test , a test of physical fitness, as well as occupational and health economic outcomes". [9] The addition of CBT to patient's medical care did not lead to improvements in any of the objective outcome measures, while the addition of GET led to a statistically significant improvement only for the six minute walking test, with this improvement failing to reach the criteria for clinical significance used for other outcome measures in the trial.</p>	<p>When actometer data was available in an included trial, then it was reported as a measure of function.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2		(continued) It is important that evidence is collected and assessed independently of the preferences of those researchers who may have ideological, professional or financial interests in the promotion of particular treatments. Data from the above trials showing no improvement in activity levels [7] and neuropsychological performance [10] should be assessed and fed into the findings of this review, even if it is presented in a way which would allow it to be excluded. The decisions to class questionnaire scores as outcome measures, and objective measures of activity as merely a way of assessing mediators of efficacy merely reflects the preferences of the researchers involved, and one could just as easily choose to present things the other way around.	When actometer data was available in an included trial, then it was reported as a measure of function.
Public Reviewer #7	Methods	Activity levels as measured objectively by actigraphy have demonstrated that CBT which incorporates GET does not increase the illness-induced decreases in physical activity. This provides important context to the 'rehabilitation' model of CFS and the expectations of patients who do CBT/GET. The following publication is a meta-analysis of 3 trials of CBT which included GET: Wiborg JF, Knoop H, Stulemeijer M, Prins JB, Bleijenberg G. How does cognitive behaviour therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity. <i>Psychol Med.</i> 2010 Aug;40(8):1281-7. PMID: 20047707. http://www.ncbi.nlm.nih.gov/pubmed/20047707	When activity levels were studied and data available, we included these in our outcome. Wiborg, 2010 was excluded because it was a re-analysis of trials. It was considered as background only.
Public Reviewer # 1	Methods	It is not explained what "methods" encompasses and indeed it appears that the way it is applied limits methods to scales, tests and tools... not history, application of case definitions, ruling out of other conditions. Reference in Review ES-2 p. 10 Key Question "What methods are available to clinicians to diagnose ME/CFS and how do the use of these methods vary by patient sub-groups" Question 1 a What are widely accepted diagnostic methods and what conditions are required to be ruled out ES 9 No studies evaluated a diagnostic test for ME/CFS using an adequate size and spectrum of patients and no studies demonstrated an accurate and reliable method for identifying patients or subgroups of patients with ME/CFS The only methods that are discussed are things such as the artificial neural network test (ANN), Schedule of Fatigue and Anergia for CFS (SOFA-CFS) and the SF-36. The CCC has a listing of conditions that should be ruled out, none of these are discussed in the review paper. The ICC excludes primary psychiatric disorders, somatoform disorder and substance abuse as well as noting the necessity of identifying and treating other diagnoses.	Thank you. We have made edits to the Key Question 1 wording to better clarify the meaning and have added the diagnostic exclusionary information to our report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 1	Methods	<p>Please improve transparency regarding the reasons for excluding studies from consideration. Explain what codes 2-4 involve</p> <p>There is a lack of transparency regarding exclusions – They simply note a number (as prime reason for exclusion) but it is difficult to ascertain exact reasons ... (Sleep Apnea review for instance, provides more information regarding exclusions such as why population not relevant – e.g. stroke, Alzheimer)</p> <p>Examples</p> <p>De Becker P, McGregor N, De Meirleir K. A definition-based analysis of symptoms in a large cohort of patients with chronic fatigue syndrome. J Intern Med 2001; 250: 234–40. Exclusion code 5 -- having looked at this study, it was difficult to determine why it would have been excluded</p> <p>Also Lloyd A, Hickie I, Wakefield D, et al. A double-blind, placebo-controlled trial of intravenous immunoglobulin therapy in patients with chronic fatigue syndrome. Am J Med. 1990;89(5):561-8. PMID: 2146875. Exclusion code: 5</p> <p>excluded code 2 -- Jason LA, Najjar N, Porter N, Reh C. Evaluating the Centers for Disease Control's empirical chronic fatigue syndrome case definition. J Disabil Pol Studies 2009; 20: 91-100</p>	<p>A key to the reasons for exclusion codes is provided at the beginning of Appendix D of the report. More specific inclusion/exclusion criteria can be found in Appendix B. In the methods section of the report we have attempted to clarify our inclusion and exclusion criteria.</p>
Public Reviewer # 1		<p>Were authors contacted if questions arose regarding studies? -- A. From Research Protocol –Contacting Authors: In the event that information regarding methods or results appears to be omitted from the published results of a study, or if we are aware of unpublished data, we will query the authors to obtain this information.</p>	<p>We did not contact authors as the papers did not appear to omit any information we were expecting.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 1	Methods	<p>Have the following studies been checked for relevance?</p> <p>Jason LA, Helgerson J, Torres-Harding SR, Carrico AW, Taylor RR: Variability in diagnostic criteria for chronic fatigue syndrome may result in substantial differences in patterns of symptoms and disability. Eval Health Prof 2003, 26: 3-22. (ME and CFS)</p> <p>Jason LA, Torres-Harding SR, Jurgens A, Helgerson J. Comparing the Fukuda et al. Criteria and the Canadian case definition for chronic fatigue syndrome. J. Chronic Fatigue Syndr. 2004; 12: 37–52.</p> <p>King C, Jason LA (2004). Improving the diagnostic criteria and procedures for chronic fatigue syndrome Biological Psychology 68 (2005) 87–106 (Looks at CDC definitions)</p> <p>Leonard A. Jason, Meredyth Evans, Molly Brown, Nicole Porter, Abigail Brown, Jessica Hunnell, Valerie Anderson, Athena Lerch (2011). Fatigue Scales and Chronic Fatigue Syndrome: Issues of Sensitivity and Specificity Disability Studies Quarterly (2011) Vol 31 No 1</p> <p>Keller B, Pyor JL, Giloteaux L (2014) Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO2 peak indicates functional impairment Journal of Translational Medicine 2014, 12:104 doi:10.1186/1479-5876-12-104</p> <p>Twisk FN (2014). Myalgic Encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS): The essence of objective assessment, accurate diagnosis, and acknowledging biological and clinical subgroups. Frontiers in Physiology. accessed on October 15 2014 at http://journal.frontiersin.org/Journal/10.3389/fphys.2014.00109/full</p>	<p>These studies have been reviewed to see if they meet inclusion criteria. They provide background and contextual information but do not meet criteria for inclusion.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #7		<p>There appears to be significant oversights in relation to "employment outcomes" in the Draft Report.</p> <p>Various measures are used, such as the Work and Social Adjustment Scale (WSAS). WSAS data from the PACE Trial was included under employment outcomes, but lost employment hours was not. This omitted data is in the following publication:</p> <p>McCrone P, Sharpe M, Chalder T, Knapp M, Johnson AL, Goldsmith KA, White PD. Adaptive pacing, cognitive behaviour therapy, graded exercise, and specialist medical care for chronic fatigue syndrome: a cost-effectiveness analysis. PLoS One. 2012;7(8):e40808. doi:10.1371/journal.pone.0040808. Epub 2012 Aug 1. PMID: 22870204.</p> <p>http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0040808</p> <p>The Draft Appendixes to the Draft Report indicates that this above mentioned paper was excluded because of "wrong outcomes". This was probably an oversight, because although the paper was primarily about cost-effectiveness and may have been excluded on that basis, employment and welfare outcomes were also included (and were not significantly different between the CBT, GET, SMC intervention groups). Employment outcomes and work hours are given importance in the Draft Report, so please reconsider the omission of this data.</p> <p>The PACE Trial was also the largest and best conducted study of its type and the important information about employment and welfare outcomes should not be excluded.</p> <p>Furthermore, the WSAS is not an accurate measurement of "employment outcomes", it is more about "functional outcomes". Please examine the following reference and appendix for clarification: "The Work and Social Adjustment Scale (WSAS) is a self-report scale of functional impairment attributable to an identified problem (Marks, 1986; see Appendix)."</p> <p>Mundt JC, Marks IM, Shear MK, Greist JH. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. Br J Psychiatry. 2002 May;180:461-4. PMID: 11983645. http://bjp.rcpsych.org/content/180/5/461.long</p> <p>Work and Social Adjustment Scale</p>	<p>Thank you for your comments. Although the work and social adjustment scale reflects more social adjustment than employment parameters, it has been recognized as one tool to use in measuring meaningful change in patients with ME/CFS. We have also included all the employment outcomes available in the trials.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 7		<p>(continued) Rate each of the following questions on a 0 to 8 scale: 0 indicates no impairment at all and 8 indicates very severe impairment.</p> <p>Because of my [disorder], my ability to work is impaired. 0 means not at all impaired and 8 means very severely impaired to the point I can't work.</p> <p>Because of my [disorder], my home management (cleaning, tidying, shopping, cooking, looking after home or children, paying bills) is impaired. 0 means not at all impaired and 8 means very severely impaired.</p> <p>Because of my [disorder], my social leisure activities (with other people, such as parties, bars, clubs, outings, visits, dating, home entertainment) are impaired. 0 means not at all impaired and 8 means very severely impaired.</p> <p>Because of my [disorder], my private leisure activities (done alone, such as reading, gardening, collecting, sewing, walking alone) are impaired. 0 means not at all impaired and 8 means very severely impaired.</p> <p>Because of my [disorder], my ability to form and maintain close relationships with others, including those I live with, is impaired. 0 means not at all impaired and 8 means very severely impaired.</p>	<p>Thank you for your comments. Although the work and social adjustment scale reflects more social adjustment than employment parameters, it has been recognized as one tool to use in measuring meaningful change in patients with ME/CFS. We have also included all the employment outcomes available in the trials.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 7	Methods	<p>According to the Draft Report:</p> <p>"Good-quality studies are considered likely to be valid. Good-quality studies clearly describe the population, setting, interventions, and comparison groups; use a valid method for allocation of patients to interventions; clearly report dropouts and have low dropout rates; use appropriate methods for preventing bias; assess outcomes blinded to intervention status; and appropriately measure outcomes and fully report results."</p> <p>"Fair-quality studies have some methodological deficiencies, but no flaw or combination of flaws judged likely to cause major bias. The study may be missing information, making it difficult to assess its methods or assess limitations and potential problems. The fair-quality category is broad, and studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are likely to be valid, while others are probably invalid."</p> <p>Not many studies are described in the Draft Report as "good-quality". The PACE Trial was described as "good quality" but other CBT/GET trials as "fair-quality". Although the PACE Trial is larger and better conducted than other CBT/GET studies, it may not be accurately described as "good-quality" according to the criteria listed above for good quality studies: "use appropriate methods for preventing bias; assess outcomes blinded to intervention status; and appropriately measure outcomes and fully report results".</p> <p>The PACE Trial was an open-label study which did not blind its participants, providers, or assessors. The difficulties of blinding in such a trial does not negate the fact that non-blinded trials are problematic. This opens up the trial results to a range of biases, particularly when two of the tested therapies are aimed at changing participants' beliefs and perceptions about their self-reported symptoms and impairments, and when the more objective outcomes do not support the self-reported improvements. This is not to say that the PACE Trial has no value and should not be included, but questions the elevation of its status to "good quality" when the same would not be done to non- blinded pharmacological trials.</p> <p>Many of the pre-defined outcomes in the PACE Trial protocol (URL below) have been greatly altered or have not been published: http://www.biomedcentral.com/1471-2377/7/6</p>	<p>Thank you for your comments. We agree that there are some limitations to the PACE trial and have expanded our discussion to reflect this throughout the report. That said, we continue to rate this as a methodologically good-quality trial (referring to internal validity). Blinding to intervention by the patient or the provider would not be feasible in this type of study; however, the assessors were appropriately blinded and primary outcomes were reported.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #40	Methods	<p>The AHRQ Evidence Review suffers from massive misunderstanding of the term “Chronic Fatigue Syndrome” (CFS) and the condition it describes. The reviewers accept application of the CFS term indiscriminately, confusing a wide range of disease definitions to great harm. They not only mix apples and oranges, but also papayas, mangos, gooseberries and parsnips. Accuracy and specificity are needed. The following distinctions must be understood and included.</p> <p>This term “Chronic Fatigue Syndrome” (CFS) originated with the CDC in 1988. It was coined to describe specifically the disease and symptoms as presented in the devastating and incomprehensible outbreak that afflicted more than 300 persons in and around the semi-rural Lake Tahoe resort of Incline Village, Nevada, beginning in the winter of 1984-85.</p> <p>In 1988 U.S. officials assembled medical experts to assign a name to the Incline Village disease. Clinicians who have previously treated the disease then known as Myalgic Encephalomyelitis (M.E.) immediately recognized the symptoms and presentations as such.</p> <p>The name Myalgic Encephalomyelitis originated in a 1950s article in the British Medical Journal (BMJ), which concerned itself with a recent outbreak at London’s Royal Free Hospital.</p> <p>This name was made official in 1968 by the World Health Organization (WHO) which concurrently defined the disease as neurological. Subsequently it would be further established that the Tahoe-area outbreak and thousands upon thousands more cases in the United States and abroad also comprised Myalgic Encephalomyelitis (M.E.)</p> <p>Nonetheless, the CDC re-christened the Nevada outbreak of Myalgic Encephalomyelitis with the wholly misleading name “Chronic Fatigue Syndrome.” The expression “chronic fatigue” conjures up for most people the universal over-tiredness of the modern era – something a long sleep and a week in the country would be bound to cure. Thus the re-christening has had the effect of causing severely incapacitated patients to be characterized as hypochondriacs and malingerers, and, most importantly, to be deprived of medical research and care. Further, the term “chronic fatigue” is unhelpfully unspecific. Fatigue is a universal byproduct in mankind’s biological struggles. Chronic fatigue is widely recognized in cancer, multiple sclerosis, infections, pregnancy and more.</p> <p>Worse yet, because of this erroneous name one million American citizens have been deprived of federal government protections to which they are entitled; notably, seriously undertaken research and implementations to be carried out by the NIH and the CDC.</p>	<p>Given that both terms have been used in the literature and continue to be used clinically, we have used them as a single term consistent with the P2P meeting. We have also attempted to shed light on how the case definitions that are associated with these terms may reflect distinct symptom sets (see Key Question 1).</p> <p>Additionally, we have added language in the introduction, discussion, and future research areas of the report to indicate the desire of the ME/CFS community and patients to adopt the term ME rather than CFS which is considered too non-specific a term.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 40	Methods	<p>(continued) In truth Myalgic Encephalitis – which is what patients suffer, despite the re-naming – features immune systems gone haywire, neurological systems and brains perennially plagued by a person’s own immune systems, dysregulating and de-regulating of hormones and body energy production systems. Pathogens and toxins appear to set off this miserable cascade. All of the dsDNA viruses are implicated, especially HHV-6 and Epstein Barr, along with parvovirus-19, mycotoxins and more.</p> <p>Whatever the cause, the patient loses cognitive function, memory, and concentration. Pain can be terrible and endless. Orthostatic dysfunction unsteadies one’s efforts to sit and stand. Above all, M.E.’s singular and defining symptom is that exertion, more often physical but also mental, will be followed by body and brain failing to recover function within normal parameters. Shortfall in cellular energy production may be involved, but research has not been funded. In any event this key identifying phenomenon is known as “post-exertional malaise” (PEM.) (Please note that “collapse,” not “malaise,” is the real issue.)</p> <p>Thus fit and capable citizens become transformed by the disease into the equivalent of broken down jalopies -- sans spark plugs, sans gasoline, sans hope. Gone is their ability to function as productive members of society and participants in family and community life. In hard dollars the cost to the United States alone is estimated at \$40 billion annually in lost productivity.</p> <p>Key to the CDC’s mis-naming was ignorance. Following the 1984-85 outbreak, local doctors eventually prevailed on the CDC to send two staffers up the Sierra Nevada to take a look in late 1986. But the CDC’s effort was de minimis. No decent university department of epidemiology would recognize it as such. The Epidemic Intelligence Service officer assigned the job walked out after a week. His rooky assistant stuck it another week, but could manage only scanty study of patients. Nor was further research ever conducted at Incline Village or sites of other extensive outbreaks, such as Lyndonville N.Y.</p> <p>At the same time, the Incline Village outbreak attracted a cloud of fierce political pressure. Everyone from local Chamber of Congress to political representatives wanted the thing to just go away; as second choice they discouraged talk of serious disease in order to preserve Tahoe’s reputation as a safe tourist destination. In addition, some observers allege that insurance companies resisted official naming of yet another serious bio-medical disease to follow the expenses of HIV-AIDS.</p>	<p>Given that both terms have been used in the literature and continue to be used clinically, we have used them as a single term consistent with the P2P meeting. We have also attempted to shed light on how the case definitions that are associated with these terms may reflect distinct symptom sets (see Key Question 1).</p> <p>Additionally, we have added language in the introduction, discussion, and future research areas of the report to indicate the desire of the ME/CFS community and patients to adopt the term ME rather than CFS which is considered too non-specific a term.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 40	Methods	<p>(continued) All in, almost everyone presenting with the Incline Village malady, like so many other diseases, complained of being excessively tired. That made it ever so easy for CDC to wrongly assign the label “Chronic Fatigue Syndrome” (CFS) to hundreds, and then thousands, and ultimately hundreds of thousands, of cases of Myalgic Encephalomyelitis.</p> <p>But this re-christening alone need not have led to tragedy – tragedy for one million or more Americans and roughly 17 million persons more worldwide. After all, much re-naming goes on without causing much harm, other than re-printing stationary and re-identifying financial accounts.</p> <p>For example, consider a person named Judy Jones. On marrying Bob Smith, Judy might well henceforth take the name Judy Smith. Nonetheless, our Judy will be the very same person-- same appearance, same bank account, same faults, and same Mom and Dad.</p> <p>But imagine the outcome if Judy, shortly after marrying Bob, were to then fall prey to identity theft. Other persons and entities could begin presenting themselves here, there and everywhere as Judy Smith. Someone or something bearing the name Judy Smith might suddenly charge thousands in computer games on a Visa card. Judy Smith seems to be a computer freak, after all, not a newlywed! But then in the Cayman Islands someone named Judy Smith opens a bank account into which pour millions of dollars each month. Judy Smith is no newlywed, but rather the hard-bitten leader of a Columbian drugs cartel!!! Subsequently there may emerge Judy Smith the porn star, Judy Smith the teenage runaway, Judy Smith the astrologer, and...</p> <p>So it was with “Chronic Fatigue Syndrome.” A very long and complicated story attaches to the evolution of the British versions of “CFS,” constructed by a small but powerful group of psychiatrists. However identity theft – the theft of the American name and its assignment to new psychological conditions of their own creation -- was the first and crucial step towards the “CFS” empire of fame and fortune which they would eventually build.</p> <p>The British versions began with elaborate theorizing rather than the empirical data, however paltry, that the American naming had relied on. Their theory asserts that “false beliefs” and “deconditioning” lay behind the complaints of unwellness accompanied by fatigue which Britain’s general practitioners (GPs) were likely to hear. The theorizing sprung fully formed from a psychiatrist’s imagination, rather like Athena from Zeus’ head. While quite legally appropriating the untrademarked name of Chronic Fatigue Syndrome, they named two new definitions for their creation “Oxford Definition” and “London Definition.”</p>	<p>Given that both terms have been used in the literature and continue to be used clinically, we have used them as a single term consistent with the P2P meeting. We have also attempted to shed light on how the case definitions that are associated with these terms may reflect distinct symptom sets (see Key Question 1).</p> <p>Additionally, we have added language in the introduction, discussion, and future research areas of the report to indicate the desire of the ME/CFS community and patients to adopt the term ME rather than CFS which is considered too non-specific a term.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 40	Methods	<p>The AHRQ Evidence Review must reflect that neither is to be considered in any way synonymous with the “Chronic Fatigue Syndrome” derived from the Incline Village outbreak of Myalgic Encephalomyelitis, and laid out, albeit imperfectly, in the Fukuda definition.</p> <p>The U.K. - invented definitions of “CFS” do not involve immune dysfunction, neurological symptoms. infections, sore throats, swollen glands, new headaches, or myalgias, all of which are cited in the U.S. disease. Most important, they do not recognize Post-exertional Malaise (PEM.) Mainly it seems they are characterizing clinical depression not previously diagnosed.</p> <p>“But how is this possible,” a person might well ask. Happily for the U.K. psychiatrists, artifacts of National Health System (NHS) regulation and custom, such as tight limits on expensive testing, allow the erroneous definitions to persist. Once a patient is labeled with the “CFS” definition they may not be investigated for other ailments. They will not receive any treatment other “activity management” relying on CBT and GET. When an adult patient refuses such “treatment” he or she sometimes finds himself “sectioned,” meaning committed to a mental hospital. A parent who differs on “CFS” care with the NHS will often have to mount a legal battle or see the child taken into care.</p> <p>One result for the U.K. has been a recent paper that reported at least one third of persons identified as having CFS by the NHS in fact are suffering from other diseases, such as Behcet’s syndrome, that might have been relieved with proper treatment. This may save money for the NHS (or not – see below) but it stands to cost the Exchequer enormously from livelihoods lost.</p> <p>Yet the psychiatrists have managed to establish and fortify their versions of “CFS,” even internationally, by running many trials of their proposed treatments – Cognitive Behavioral Therapy (CBT) and Graded Exercise Therapy (GET.) The manipulation of data is an old art, and these psychiatrists sliced and diced their trials so that they resulted in a great many papers, approved by close colleagues at U.K.-based medical journals. The numbers helped them climb in important computer-based grading of research according to numbers of citations, and allowing them to become quite eminent despite scant real research. Political connections and a concurrence of interests with the benefits-cutting government of Prime Minister Tony Blair helped them to extensive funding and national eminence. The \$8.7 million Pace Trial was the consummation.</p>	<p>Thank you for your comments. We appreciate your concerns and have attempted to clarify these issues in our discussion. We agree that there are some limitations to the PACE trial and have expanded our discussion to reflect that thorough the report. We have also considered other treatments and interventions when studies provided these results.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 40	Methods	<p>And so Britain's Medical Research Council held a press conference to announce the trial's completion. The world's press was invited and attended with interest. The MRC press release declared the trial a great success proving the worth of CBT and GET for "CFS". The world press duly reported the contents of the press release. Having no way of knowing that "London" and "Oxford" brands were the syndromes under study, and that Fukuda-defined "CFS" had little in common, they reported an upbeat outcome to world attention. Indeed, confusingly, these continue to be the prescription even of the U.S. CDC on its web page – though of course it does not reflect any trial of the disease one might call by the name "CFS" in the US. (The relationship and influence of UK psychiatrists during the 20 year-long tenure of William Reeves as CDC's "CFS" chief is relevant, but too complicated and not necessary to these comments.)</p> <p>It is likely that the PACE trial will be proved fraudulent and retracted in the long run. Thus for the AHRQ Evidence Review to heavily weight and indeed propagate its fraudulent message in defining the future research goals of the United States of America would seem to be irresponsible if not illegal in respect of the interests of US citizens and taxpayers.</p> <p>Meanwhile British investigators are being held off from the raw data by refusals of participating institutions to meet FOIA requests. The British establishment as usual has reflexively closed ranks in the first instance, and a court decision failed to support the FOIA request. But it is early innings, and Britain's traditional favorite spectator sport, cricket test matches, can go on for days.</p> <p>Psychiatrists belonging to the "CFS" clique meanwhile are thriving on the dividends from "Oxford CFS" and "London CFS." A private company part-owned by one or more is earning a great deal of money from contracting to supply CBT and GET services to private insurers and the National Health Service alike. The company is registered in Hamburg, Germany, so little may be learned about its business. But NHS staff have calculated that the cost is turning out to be a great deal more than anticipated. The Blair government's embrace of the doctrines of CBT and GET is not working out well for the U.K. financially. Nor has it worked out for the patients – they have not returned to work and school.</p> <p>This AHRQ Evidence Review is meant to provide an agency of the United States government guidance in researching for the interests and welfare of the citizens of the United States. The very heavy weighting of dubious and specious work by British psychiatrists, using definitions entirely at odds with U.S. medical descriptions of the disease, has hopelessly compromised the review.</p> <p>I conclude in noting that the extensive threats to the interests of American citizens by errors, omissions and erroneous weighting of data contained within the AHRQ Evidence Review stand are well-explicated in the Comments submitted by Mary Dimmock, Jennie Spotila, et alia. I endorse their explanations and insights</p>	<p>We agree that there are some limitations to the PACE trial and have expanded on these in our discussion of this trial. We also appreciate that there are limitations to using different case definitions. It is truly our goal to review what evidence is available and to inform the P2P about limitations and applicability of previous research and indicate focus areas for future research.</p>

Commentator & Affiliation	Section	Comment	Response
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Methods	<p>Compounding this flawed assumption are the a priori choices in the Review Protocol that ignored critical questions and instead focused on a narrowly defined set of questions and applied restrictive inclusion and exclusion criteria. As a result, evidence that would have refuted these flawed starting assumptions or that was required to accurately answer the questions was never considered. The Evidence Review must discuss the substantial evidence that refutes its assumptions that the eight CFS and ME definitions represent the same or closely related disease(s) and that that disease is a valid clinical entity linked together by medically unexplained fatigue.</p> <p>The Review fails to prove the validity of the assumption that the eight CFS and ME definitions represent the same disease or group of closely related diseases centered around “medically unexplained chronic fatigue.” But more importantly, the Review ignores the substantial evidence in the literature that demonstrates this assumption to be false. In analyzing diagnostic methods, the Review focuses solely on the accuracy of the given diagnostic method itself as it applies to a given definition. The assessment of diagnostic methods ignores evidence of the lack of accuracy of the underlying definition and the resultant implications for the validity of the diagnostic method or its applicability across all CFS and ME case definitions</p>	<p>We appreciate that the case definitions are very different and that some are more inclusive than others and may reflect less severe cases or non-cases of ME/CFS as is fully outlined in the Key Question 1 response of the report. After consultation with the Working Group and Technical Expert Panel, we elected to include all case definitions in the report a priori for several reasons. First, there are very few trials and excluding some of these definitions would limit the evidence even further than is already outlined. Second, the intent was that this could at least provide a foundation to determine what interventions may be effective. Where available, we compared findings using different case definitions to determine if findings were consistent or not across studies. We have expanded the future research needs discussion to indicate that future studies should perform sensitivity analysis to determine differences between case definitions as well as subgroups of patients that meet different criteria. We have elected to use the term ME/CFS at the outset of the report in order to not risk missing important and/or informative evidence that may be labeled under one term or another. By using these terms synonymously throughout the report, we are not endorsing or refuting that these labels reflect the same disease state. We are hopeful that the evidence reported under research question one will help to shed light on this controversial topic for the P2P workshop.</p>

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Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Methods	(continued)	(continued) Additionally, we have added language in the introduction, discussion, and future research areas of the report to indicate the desire of the ME/CFS community and patients to adopt the Canadian Carruthers case definition rather than the more non-specific CFS case definitions
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Methods	By choosing to not include the PubMed database in the search, it seems a number of relevant studies have been overlooked. Source: http://www.cortjohnson.org/blog/2014/10/15/ahrq-report-excluding-progress-exclusionary-factors-missing-studies	Studies that would be in Pub Med specific to our Key Questions would also be found in Medline and the other databases searched.
Public Reviewer # 1	Methods	The review treats all definitions as if they are describing the same disease. The conclusions ignore the very shortcoming it highlights elsewhere – that is, that some definitions (Oxford in particular) may inappropriately include patients that would not otherwise be diagnosed with ME/CFS and may provide misleading results. Reference in Review -- ES-29 Applicability “We elected to include trials using any predefined case definition but recognize that some of the earlier criteria, in particular the Oxford (Sharpe, 1991) criteria, could include patients with 6 months of unexplained fatigue and no other features of ME/CFS. This has the potential of inappropriately including patients that would not otherwise be diagnosed with ME/CFS and may provide misleading results.” (emphasis added)	We appreciate that the case definitions are very different and that some are more inclusive than others. When possible we compared findings using different case definitions to determine if findings were consistent or not across studies.

Commentator & Affiliation	Section	Comment	Response
Mary Dimmock et al	Methods	<p>Compounding this flawed assumption are the a priori choices in the Review Protocol that ignored critical questions and instead focused on a narrowly defined set of questions and applied restrictive inclusion and exclusion criteria. As a result, evidence that would have refuted these flawed starting assumptions or that was required to accurately answer the questions was never considered. Some examples of how these assumptions and protocol choices negatively impacted this Evidence Review include:</p> <p>Evidence about the significant differences in patient populations and in the unreliability and inaccuracy of some of these definitions was ignored and/or dismissed.</p>	<p>We appreciate that the case definitions are very different and that some are more inclusive than others and may reflect less severe cases or non-cases of ME/CFS as is outlined in the Key Question 1 results in the report. After consultation with the Working Group and Technical Expert Panel, we did elect to include all case definitions in the report a priori for several reasons. First, there are very few trials and excluding some of these definitions would limit the evidence even further than is already outlined. Second, the intent was that this could at least provide a foundation to determine what interventions may be effective. Where available, we compared findings using different case definitions to determine if findings were consistent or not across studies. We have expanded the discussion of our future research needs to include that future studies should perform sensitivity analysis to determine differences between case definitions as well as subgroups of patients that meet different criteria. We have elected to use the term ME/CFS at the outset of the report in order to not risk missing important and/or informative evidence that may be labeled under one term or another. By using these terms synonymously throughout the report, we are not endorsing or refuting that these labels reflect the same disease state. We are hopeful that the evidence reported under research question one will help to shed light on this controversial topic for the P2P workshop.</p>

Commentator & Affiliation	Section	Comment	Response
Mary Dimmock et al	Methods	Compounding this flawed assumption are the a priori choices in the Review Protocol that ignored critical questions and instead focused on a narrowly defined set of questions and applied restrictive inclusion and exclusion criteria. As a result, evidence that would have refuted these flawed starting assumptions or that was required to accurately answer the questions was never considered. Some examples of how these assumptions and protocol choices negatively impacted this Evidence Review include: Evidence about the significant differences in patient populations and in the unreliability and inaccuracy of some of these definitions was ignored and/or dismissed.	(continued) Additionally, we have added language in the introduction, discussion, and future research areas of the report to indicate the desire of the ME/CFS community and patients to adopt the Canadian Carruthers case definition rather than the more non-specific CFS case definitions.
Public Reviewer #54	Methods	In order to find abstracts and articles the AHRQ searched three main databases using the terms fatigue Fatigue Syndrome Chronic and Encephalomyelitis. With the notable exception of PsycINFO a database of abstracts of literature in the field of psychology produced by the American Psychological Association these are the same databases used by the Drug Class Review Drugs for Fibromyalgia Final Original Report published by the Oregon Health Science University in 2011. Ovid and EBMCochrane are large medical databases though they dont necessarily include every study conducted on a given illness or condition. Only controlled trialsare included in the Cochrane databases.The most glaring problem with the search is that it included studies on fatigue. Indeed a number of studies included in the review were on fatiguing illnesses rather than MECFS. Like the introduction the search reflects a state of confusion on the part of the authors. The confusion is not altogether surprising given that researchers also appear to be confused about the difference between CFS and chronic fatigue. Nonetheless experts in the field are not confused. They are aware that while ME has been used abroad since the 1950s it has not been used as a diagnosis here in U.S. Specialists have been limited to CFS as a diagnosis like it or not.A second problem is that with the perennial lack of NIH funding for MECFS controlled trials much of the information about treating the disease is based on clinical observations. None of these were included. nor were studies that were controlled but which did not meet the set of criteria for inclusion in the review such as addressing the Key Questions. See more at http://cfstreatment.blogspot.com 2014 09 the ahrq draft report fundamentally and.html sthash.tZkIXvLH.dpuf	Thank you for your comments. We have expanded our discussion of the comparison between case definitions as well as the limitations revolving around the use of different case definitions for trial inclusion.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 41	Methods	TOP 10 TESTS for MYALGIC ENCEPHALOMYELITIS CFS LABELED PATIENTS Contents TEST 1 CardioPulmonary Exercise Testing with measurement of VO2 max anaerobic threshold and maximal heart rate and respiration. TEST 2 Brain neuro SPECT PET scans and MRI brain scan TEST 3 Mitochondrial Dysfunction TEST 4 TH1TH2 imbalance TEST 5 Natural Killer Cell Function Activity testing TEST 6 abnormalities of the 25A pathway RNaseL ratio TEST 7 Virology TEST 8 Heart Function TEST 9 Neurocognitive testing sleep studies TEST 10 Endocrine testing CommentaryAdditional References Poor mans tilt table testing description	Thank you - noted.
Public Reviewer # 43	Methods	By focusing on symptom related outcomes for fatigue alone the Evidence Review excluded consideration of postexertional malaisePEM probably the most devastating effect of the disease for me.PEM is the hallmark symptom of MECFS the is universally present in patients with this disease. This symptom can be reliably replicated with 2 day exercise testing.	Thank you for your comments. The diagnosis and treatment of PEM specifically was beyond the scope of the questions designed by the planning committee.
TEP Reviewer #1	Results	There is no mention among the treatments of the rituximab RCT. Why is that?	Thank you for this question. The study on rituximab was < 12 weeks in duration and thus did not meet our inclusion criteria. However, we performed secondary searches to identify interventions that would typically be given for a duration of <12 weeks, but had outcome data extending 12 weeks or longer. The results of our search identified this trial of rituximab (and a trial of acyclovir). These have been added to the discussion section.
TEP Reviewer #2	Results	Amount of detail is sufficient. Clarity and organization are good.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Results	Omission: Page 19. What harms are associated with diagnosing ME/CFS? Stigmatization could be considered a “harm” of diagnosing ME/CFS as stated here. But it should be clarified that receiving the diagnosis per se does not do harm. Actually patients feel a sense of validation from the diagnosis, that their symptoms have been legitimized in the form of the diagnosis given by a physician. That is positive validation, not harm. Also physicians are reluctant to give the diagnosis as they think it perpetuates the illness—a concern without supporting evidence. So this is a more complex issue than is stated here—stigmatization is only one aspect of potential harm. I would not leave the erroneous impression that doctors should not use the diagnosis. The diagnosis is validating, not harmful to the individual patient.	Thank you for this comment. We have made changes to this section to highlight that although some patients report relief with a diagnosis of ME/CFS, we did not find studies to reflect this patient experience.
TEP Reviewer #3	Results	The authors state that multiple case definitions exist. However they describe the classification accuracy delivered with a nonlinear black-box model (artificial neural network) without clarifying which case definition was used as the gold standard. Was this classification evaluated based on the Fukuda case definition? This should be stated clearly. It also appears circular in logic to create classification models based on the same symptoms that were directly or indirectly used to perform the original class assignment e.g. fatigue. I would recommend an emphasis on those studies that were based on a selection of biomarkers, blood-borne or other. In the end however, I agree that none of these have been extensively validated.	We have revised the text to better describe the case definitions used for each study. It is true that for the diagnosis of ME/CFS, the case definition method is the accepted strategy for diagnosis, but no one case definition has been agreed upon by consensus in the literature.
TEP Reviewer #3	Results	The exclusion of studies featuring molecular assays on the basis that classification statistics were not reported is very unfortunate. The authors could have applied the same methodology as in that used in the analysis of outcomes in the intervention studies, that is to report the pooled weighted mean differences. At the very least the inclusion of these studies would provide a qualitative indication of which parameters a clinician may want to pay attention to and whether these might be abnormally high or low. Certainly a statement of consensus across such studies would be of interest to the reader. I would encourage the inclusion of such a table in the appendices.	We acknowledge that our approach was intended to review the literature evaluating diagnosis using case definition strategies. We did not evaluate etiology-based diagnosis because there has not been an agreed upon etiology for ME/CFS.
TEP Reviewer #3	Results	As the authors state that many more women than men appear afflicted with CFS, it may be appropriate to include in Table A the specific gender composition of the cohorts instead of simply the overall number of subjects. Another very pertinent information would be the median years ill in each of these cohorts.	When this information is available we have provided it.
Peter White Queen Mary University of London, UK	Results	Also of relevance to the potential harm consequent upon being given a diagnosis of CFS or ME, one large primary care prospective study suggested there might be a difference in prognosis depending on which particular diagnostic label was given, although this was not a randomised study (Hamilton et al, 2007). This subject has been well reviewed by Huibers and Wessely (2006).	This study was examined and provided only background information.

Commentator & Affiliation	Section	Comment	Response
Peter White Queen Mary University of London, UK	Results	There are several other studies of misdiagnoses in patients diagnosed with probable or definite CFS/ME that you might want to consider (Lawn et al, 2010; Newton et al, 2010; Devasahayam et al, 2012; Brimmer et al, 2013). The latter three studies show that between 40 and 50% of patients with a provisional or definite diagnosis of CFS/ME have alternative diagnoses.	Thank you. We have accessed these references and will include them in the harms section. In most cases they are not studies of diagnosis per se, but case series that demonstrate how important the careful exclusion of other explanatory diagnoses is to the diagnosis of ME/CFS.
PD White, T Chalder, R Moss-Morris, M Sharpe, AJ Wearden	Results	We examined non-serious adverse events (NSAEs) and other safety measures in the PACE trial in more detail in Dougall et al, 2014. The number of NSAEs did not differ between treatment arms either when considered as a whole (table 1) or when only considering NSAEs attributed to CFS (table 2). Table 5 in this paper shows there were no differences across the four treatment groups in the proportion of patients reporting deterioration in fatigue (one of the primary outcomes) after treatment. On the second primary outcome, physical function,, a significantly greater proportion of patients showed deterioration after APT (25%) and r SMC (18%) than after CBT (9%) or GET (11%)(table 5).	Thank you - we have accessed this paper and incorporated it into our analysis and interpretations.
PD White, T Chalder, R Moss-Morris, M Sharpe, AJ Wearden	Results	Page 21 "...and almost half of patients assigned to physiological exercise testing (10/25) refused to repeat testing at follow-up over concern for harm." This refers to Moss-Morris 2005, but the physiological exercise testing was an outcome measure, not part of GET. You do not mention that 12/24 participants in the control arm also declined exercise testing, compared to 11/25 participants receiving GET (Table 4). Only 3 participants dropped out after GET compared to 3 in the control arm. We think you should consider revising your interpretation of these data as evidence of harm of GET.	We have clarified this information in the results section where we discuss this study; about half of all participants declined to repeat the second exercise test.
Peer Reviewer #2	Results	This reviewer appreciates the Systematic Review Team's interpretation of the evidence as it relates to very popular graded exercise and cognitive behavior therapy approaches. The results of graded exercise therapy and cognitive behavior therapy have not been universally positive, as the Review Team points out methodologically, but the commonality of this approach in clinic has more to do with the quality of evidence than the magnitude of effect. There also have been numerous reports in the patient community about very unpleasant consequences that resulted from non-compliance with treatment recommendations, particularly in Great Britain where the National Health Service has codified cognitive behavior therapy and graded exercise therapy as a gold standard intervention. One important contribution is to provide some additional evidentiary context for these recommendations.	Thank you - we have added information in our results section to provide more context around these interventions and their benefits and limitations.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Results	This reviewer also appreciates the emphasis the Review Team placed on pointing out the social stigma experienced by people with ME/CFS. The discussion of the nascent literature regarding the psychosocial burden of diagnosis, including stereotyping and bias on the part of biomedical and mental health practitioners, can begin to promote a culture of humility and compassion among clinicians who encounter individuals with atypical symptoms and signs. Although the literature has yet to specifically document this in individuals with ME/CFS, bias and stereotyping leads to disparate health outcomes elsewhere in biomedicine; one can easily surmise that bias against individuals with ME/CFS can lead to the same patterns of recalcitrant health disparities and inequities.	Thank you for your comments.
Peer Reviewer #2	Results	The comparison between cognitive behavior therapy and the mixed category of no treatment, adaptive pacing, and support is conceptually challenged by the fact that cognitive behavior therapy may include adaptive pacing and support. Indeed, the trials that report the use of cognitive behavior therapy often do not report what specific treatment modalities were used. Treatment intensity is often different between groups and across studies in the cognitive behavior therapy literature, as well as the inclusion of exercise as a cognitive behavior therapy modality. The overlap between the various different groups and potential for more time spent with patients receiving cognitive behavior therapy leaves open the possibility that the small observed pooled treatment effects were related to attention bias and the non-significant differences were related to overlap between treatment conditions.	Most of the trials included a group that received some form of attention; however, we have attempted to evaluate the studies based on their comparisons to see if an attention bias exists. We have added this information where applicable.
Peer Reviewer #2	Results	An issue of additional substantial importance is the potential variation in treatment effectiveness based on the type of classification system that was used in each study. Early classification systems, such as the Oxford system, do not adequately exclude individuals with fatigue related to depression. Depression has been documented to respond favorably to aerobic exercise (i.e., graded exercise therapy). However, this reviewer's clinical experience has been far more mixed. It is possible that early trials of graded exercise therapy that used the Oxford criteria mixed likely responders and non-responders in a manner that trials using other criteria might not. It may be worth a subgroup analysis in the systematic review to determine whether there is substantial variation in results based simply on classification system used to identify ME/CFS.	We have reviewed the outcomes of the trials based on which case definition was used, and added this information to the text where applicable. We have expanded on the limitations of the review in the discussion section.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Results	Graded exercise therapy sets up a self-fulfilling prophecy in which subjects might report increased activity frequency and concomitant improvement in physical functioning, but that this improvement is an artifact rather than a beneficial effect of the treatment itself. The papers by Black & McCully are instructive in this regard. Although the authors initially reported a graded exercise approach increased activity as measured by accelerometry, their subsequent 'clarification' paper revealed that the increase in activity was not likely meaningful to the patient's function and quality of life. Extrapolating these findings to large studies of graded exercise therapy is important, because findings of improvement should be taken with caution unless there is (1) objective verification of subject self-report and (2) care secondary analysis of objective activity data, particularly in light of the attrition associated with some graded exercise studies. Black CD, O' Connor PJ, McCully KK. Increased daily physical activity and fatigue symptoms in chronic fatigue syndrome. <i>Dyn Med</i> . 2005 Mar 3;4(1):3. PMID: 15745455 Black CD, McCully KK. Time course of exercise induced alterations in daily activity in chronic fatigue syndrome. <i>Dyn Med</i> . 2005 Oct 28;4:10.	These studies were reviewed for inclusion and were <12 weeks long, so were not included in the results section. We have expanded our discussion section to address the limits of the research.
Peer Reviewer #2	Results	Page 57, Line 18: Cardiopulmonary exercise testing as a biomarker could be considered here. There are several studies to support the discriminative validity of volume of oxygen consumed at peak and anaerobic threshold, as well as other cardiac, pulmonary, and metabolic measurements, as well as aberrant subjective recovery responses among individuals with ME/CFS compared to control subjects without ME/CFS. Although this area of the literature remains nascent, this type of testing is cheaper, more plentiful, and seems more favorable than the serum and plasma markers presently listed.	Thank you for your comment. No specific studies were identified by the reviewer, and we did not find any studies to include that would have met our inclusion criteria.
TEP Reviewer #4	Results	The detail in the tables is helpful and appropriate. The studies are clearly described. The messages are explicit but not readily applicable.	Thank you - we have attempted to indicate the applicability in the section labeled as such and included key features in the tables, such as case definition.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	Results	The authors acknowledge "The results suggest that the CFS criteria captures a broader population, and that ME or ME/CFS criteria identify subsets with greater severity of symptoms from among the CFS group." Yet, the theme that the different definitions have the potential to select entirely different populations is not taken into account when rating the studies. For example the PACE study which received a good rating likely will not compare with studies requiring post-exertional malaise. Study participants with greater symptom severity were likely excluded in this cohort. It is noted that the Oxford definition may include only patients with the symptom of fatigue. The International Association of CFS/ME, the professional scientific association for the syndrome has determined that post-exertional malaise is a required symptom for diagnosis. This is stated in the guidelines for "Chronic fatigue syndrome/myalgic encephalomyelitis. A primer for clinical practitioners." which can be found on the National Guidelines Clearinghouse: International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME). Chronic fatigue syndrome/myalgic encephalomyelitis. A primer for clinical practitioners. Chicago (IL): International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME); 2012. 41 p. [121. references] http://mc.manuscriptcentral.com/ehc?URL_MASK=0f3534e90eee41c99adebe3242213fbc .	Thank you for your comment. The quality of the study was determined by evaluating key methodological criteria that are pre-defined for systematic reviews. The case definition used for inclusion was not part of the quality rating criteria. We expanded the limitations of the review section in the discussion to address the differences in case definitions used in the intervention trials.
TEP Reviewer #4	Results	Given that the experts on this consensus document chose a definition (Canadian Clinical, 2003) that requires post-exertional malaise as a requirement and that is listed on ARHQ's own website, a logical conclusion is that not all case definitions are created equal and that a more extensive discussion of case definitions with limitations related to subject selection would strengthen this section. Overall, the section on CBT/GET was handled well save for the case definition limitation.	Thank you - we have clarified this in the discussion.
TEP Reviewer #4	Results	Please consider clarifying the section on harms associated with diagnosis. It appears that the report suggests that a diagnosis of ME/CFS is harmful to patients and may discourage clinicians from making a diagnosis, when that may not be the authors intent.	Thank you - we agree and, to the extent supported by the evidence, we have expanded the discussion of potential for benefit from being diagnosed.
Peer Reviewer #4	Results	Results: not scientifically discernable	Thank you for your comment. We have clarified the results section to make this more discernable.
Peer Reviewer # 5	Results	With regard to treatment, the severe exclusion criteria have eliminated one of the most promising recent reports. Rituximab was given to small group of patients, with remarkable effect in some. But rituximab is not given for 12 weeks—is this why it was excluded? http://www.ncbi.nlm.nih.gov/pubmed/22039471	We limited our interventions to at least 12 weeks duration due to the cyclical nature of ME/CFS. In the discussion we mention interventions that were excluded due to not being at least 12 weeks long.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 5	Results	The authors' efforts are constricted by the key questions as well as the strategy imposed to filter studies for consideration and for rating those to be studied. How useful would these requirements have been for another illness that was also psychologized—stomach ulcers. The breakthrough in the illness was an n of 1 study, in which a single person infected himself with H. pylori, then cured himself with antibiotics. This study would be excluded even if the sample size had been larger, because 12 weeks of antibiotics were not needed. Furthermore, it was sufficient to demonstrate that assay for H. pylori could diagnose stomach ulcers, and this is now used as a first step, non-invasive way to determine whether an individual's stomach pain might be due to an H. pylori-derived ulcer.	We did not limit study inclusion by sample size. We have conducted a separate search to locate any studies with an appropriate pharmacological intervention of <12 weeks. For viral therapies we added one trial on acyclovir in our discussion section and for immune modulators we added one trial of rituximab in our discussion section. We also had two team members review the full text of all excluded studies; no analogous studies were found.
Peer Reviewer # 5	Results	Only 4 potential biomarker studies are mentioned in the executive summary (page ES-10) and are dismissed as “small, single studies”. There are far more biomarker studies than these. Undoubtedly they do not fulfill some of the criteria for inclusion, but they still could be mentioned as ones that deserve follow-up (for example, in the future research section).	Due to scope and process limits we cannot mention all studies that did not meet criteria. Please see Appendix D for our complete excluded studies list.
Peer Reviewer # 5	Results	My knowledge of the literature indicates quite a number of possible objective biomarkers; the authors did not capture the extent of this ongoing research. I show some of the relevant studies below. I did not have time to make an exhaustive search of the literature, nor did I investigate carefully whether the authors listed why they included or did not include some of these studies, though I did see that some are not mentioned anywhere in the report, suggesting they have been overlooked.	Due to scope and process limits we cannot mention all studies that did not meet criteria. Please see Appendix D for our complete excluded studies list.
TEP Reviewer #6	Results	The tabular presentation of results is generally well done but does not adequately address statistical significance vs. clinical relevance	Thank you - we have expanded our discussion of clinical relevance and meaningful change.
TEP Reviewer #6	Results	On the question of including or excluding studies, obviously I feel more of our research should have been included! I am also aware that some research that is included has been suggested questionable by at least one government agency but will say no more on that topic. One problem with such a limited sample of studies is subject bias. The same patient population is often represented in multiple studies	We have tried to highlight when studies have used the same data set so that it is obvious these are the same patients.

Commentator & Affiliation	Section	Comment	Response
<p>Jose G. Montoya, MD, FACP, FIDSA Professor of Medicine Division of Infectious Diseases and Geographic Medicine Stanford University School of Medicine</p>	<p>Results</p>	<p>Re: Randomized clinical trial cited in your report: Montoya JG., Kogelnik A.M., Bhango M., Lunn M.R., Flamand, L., Merrihew L.E., Watt T., Kubo, J.T., Paik J., Desai M. A randomized clinical trial to evaluate the efficacy and safety of valganciclovir in a subset of patients with chronic fatigue syndrome" Journal of Medical Virology. 2013; 85(12): 2101-2109. This trial is mentioned in Table 2 (Trials of medications for ME/CFS) in row 5 for "Montoya et al. 201371" To Whom It May Concern: Please correct following mistakes: 1. Our study design was randomized, double-blind, placebo controlled. This is one of the most robust designs in clinical trials and should be emphasized in your report. 2. For placebo we did not use "IV for placebo (1% albumen solution) every 30 days for 6 months (6 infusions)". That would have been clearly the wrong choice for a placebo in this study. We used a placebo-pill form that was identical to the valganciclovir pill. The information contained in your Table 2 under "Interventions" needs to be corrected. You can see in the article, in the methods section (page 2102, last paragraph under "Study Protocol and Patients"): "Patients were given VGCV or placebo based on their assignment for 6 months and followed for 6 additional months. Patients and investigators were blinded for a total of 9 months from the start of randomization and until data were collected and locked onto three CDs. The packaging of VCGV and placebo was performed by Roche at their headquarters (Basel, Switzerland) and sent to the Stanford Pharmacy. VCGV or identical-appearing placebo was initiated at a dose of 900 mg (two 450 mg tablets) twice daily for 21 days followed by 900 mg once daily to complete 6 months"</p>	<p>Noted; this information has been corrected. Thank you.</p>
<p>Jose G. Montoya, MD, FACP, FIDSA Professor of Medicine Division of Infectious Diseases and Geographic Medicine Stanford University School of Medicine</p>	<p>Results</p>	<p>3. You chose not to report other clinical endpoints that were statistically significant (but chose somewhat arbitrarily to include others that were not significant). Please add the following clinical endpoints that were statistically significant and support further the possibility of a clinical benefit in the treatment group when compared to the placebo group: MFI-20 mental fatigue subscore (P = 0.039); cognitive function (P = 0.025). You also chose to ignore that patients in the VGCV arm were 7.4 times more likely to be classified as responders (P = 0.029) before the blind codes were broken and made available to the investigators. From the article (Abstract section): "However, statistically significant differences in trajectories between groups were observed in MFI-20 mental fatigue subscore (P = 0.039), FSS score (P = 0.006), and cognitive function (P = 0.025). VGCV patients experienced these improvements within the first 3 months and maintained that benefit over the remaining 9 months. Patients in the VGCV arm were 7.4 times more likely to be classified as responders (P = 0.029)".</p>	<p>These outcomes were not included among the pre-specified endpoints for the systematic review, which includes measures of physical function and fatigue.</p>

Commentator & Affiliation	Section	Comment	Response
Jose G. Montoya, MD, FACP, FIDSA Professor of Medicine Division of Infectious Diseases and Geographic Medicine Stanford University School of Medicine	Results	4. You also decided not to report key biological-immune endpoints such as the effect of valganciclovir effect on monocytes (an unknown biological effect of this drug until it was discovered in our study), neutrophils and cytokines. These should be added. From the abstract section of the article: "In the VGCV arm, monocyte counts decreased (P < 0.001), neutrophil counts increased (P = 0.037) and cytokines were more likely to evolve towards a Th1-profile (P < 0.001)". And yes, contrary to our hypothesis and hope, we did not observe changes on the viral titers. It is important to include these biological effects since they support that CFS is a biological entity amenable to biological interventions.	These outcomes were not included among the pre-specified endpoints for the systematic review, which includes measures of physical function and fatigue.
Jose G. Montoya, MD, FACP, FIDSA Professor of Medicine Division of Infectious Diseases and Geographic Medicine Stanford University School of Medicine	Results	5. Despite the fact that you judged this randomized clinical trial as "fair" in quality, you do not mention it in your "Structured Abstract" section: "Of the 36 trials on interventions, rintatolimod improved measures of exercise performance, compared with placebo; cognitive and behavioral therapy (CBT) and graded exercise treatment (GET) compared with no treatment, relaxation or support were found to improve fatigue, function, and quality of life, while CBT also improved employment outcomes. Other interventions either provided no benefit or evidence was insufficient to draw conclusions".	Noted; the structured abstract has been revised to include this finding. Thank you.

Commentator & Affiliation	Section	Comment	Response
Jose G. Montoya, MD, FACP, FIDSA Professor of Medicine Division of Infectious Diseases and Geographic Medicine Stanford University School of Medicine	Results	6. On Table 2, this study is cited as reference 71 when it should be reference 60. Please do not hesitate to contact me should you wish to discuss above comments or seek additional information. Transparency is the key to this process as long as there is an underlying good intention to bring scientific resources necessary to solve the ME/CFS puzzle.	Noted; this information has been corrected. Thank you.
Lisa Petrison, Ph.D Executive director, Paradigm Change	Results	I would like to object to the idea that works suggesting that cognitive behavioral therapy (CBT) and graded exercise therapy (GET) are relevant to the understanding of the disease that the NIH is now choosing to call "ME/CFS." A critique of the most prominent of these studies follows. Other CBT/GET studies are characterized by these same flaws. In addition, a list of research studies looking at the physiological abnormalities that have been found in studies of patients qualifying for CFS or ME diagnoses follows. I request that these studies all be considered in any literature reviews that the NIH may conduct. In particular, this study is about the Lake Tahoe cohort, was published in a prestigious journal and was authored by respected researchers. I therefore request that it not be overlooked in the consideration of this disease. Buchwald D, Cheney PR, Peterson DL, Henry B, Wormsley SB, Geiger A, Ablashi DV, Salahuddin SZ, Saxinger C, Biddle R, et al. A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpesvirus type 6 infection. Ann Intern Med. 1992 Jan 15;116(2):103-13. PMID: 1309285	We reviewed the study for relevance and it did not meet inclusion criteria for any of our Key Questions.

Commentator & Affiliation	Section	Comment	Response
Peter White Queen Mary University of London, UK	Results	<p>There are several other studies of misdiagnoses in patients diagnosed with probable or definite CFS/ME that you might want to consider (Lawn et al, 2010; Newton et al, 2010; Devasahayam et al, 2012; Brimmer et al, 2013). The latter three studies show that between 40 and 50% of patients with a provisional or definite diagnosis of CFS/ME have alternative diagnoses.</p> <p>Also of relevance to the potential harm consequent upon being given a diagnosis of CFS or ME, one large primary care prospective study suggested there might be a difference in prognosis depending on which particular diagnostic label was given, although this was not a randomised study (Hamilton et al, 2007). This subject has been well reviewed by Huibers and Wessely (2006).</p> <p>References Brimmer, D. J., Maloney, E., Devlin, R., Jones, J. F., Boneva, R., Nagler, C. & Unger, E. R. (2013). A pilot registry of unexplained fatiguing illnesses and chronic fatigue syndrome. BMC research notes,2013; 6(1): 1-11. Devasahayam A, Lawn T, Murphy M, White PD. Alternative diagnoses to chronic fatigue syndrome in referrals to a specialist service: a service evaluation survey. Journal of the Royal Society of Medicine Short Reports 2012;3:4. DOI 10.1258/shorts.2011.011127 Hamilton WT, Gallagher AM, Thomas JM, White PD. The prognosis of different fatigue diagnostic labels: a longitudinal survey. Family Practice 2005;22:383-388. Huibers MJ, Wessely S. The act of diagnosis: the pros and cons of labelling chronic fatigue syndrome. Psychol Med 2006;36:895–900 Lawn T, Kumar P, Knight B, Sharpe MC, White PD. Psychiatric misdiagnoses in patients with chronic fatigue syndrome. Journal of the Royal Society of Medicine Short Reports. 2010;1:28. DOI 10.1258/shorts.2010.010042. http://shortreports.rsmjournals.com/content/1/4/28.full Newton JL, Mabillard H, Scott A, Hoad A, Spickett G. The Newcastle NHS Chronic Fatigue Service: not all fatigue is the same. J R Coll Physicians Edin 2010;40:304–7</p>	<p>Thank you. We have accessed these references and will include them where applicable. In most cases they are not studies of diagnosis per se, but case series that demonstrate how important the careful exclusion of other explanatory diagnoses is to the diagnosis of ME/CFS.</p>
Public Reviewer # 49	Results	<p>The impact for patients is isolation and stigma from the medical community at large. Patients have unbelievable unmet health care needs, and most of us have very clear stories of infectious trigger, without recovery. As you know, CBT does not treat HIV infections, or any other infectious process, including Ebola. GET has shown to harm ME patients. Patients do not want to be bedridden or housebound. It just happens to them because they are too sick to get out of their bed or their houses. and for those who are well enough to get out, they have learnt to pace themselves and to listen to their bodies so they don't relapse.</p>	<p>Thank you for your comment. We have attempted to highlight which interventions are targeting an underlying pathophysiological process and which are targeting symptom management. Both CBT and GET fit into the latter category.</p>

Commentator & Affiliation	Section	Comment	Response
Sister Sandra Duma, OSF, MS Ed	Results	...4) The well-known problems with the PACE trial, yet giving credence to its recommendations of CBT and GET anyway	We have added further data on harms from the PACE trial and expanded our discussion of limitations, applicability, and future research needs regarding this trial.
Charmain Proskauer	Results	<p>p. 21-22 Harms were not well reported overall, and evidence is insufficient. Patients receiving GET reported more harms compared with cognitive behavioral therapy (CBT), adaptive pacing, or usual care in one good-quality trial and almost half of patients assigned to physiological exercise testing (10/25) refused to repeat testing at followup over concern for harm. Dropout rates were greater with exercise (25/68, 37%) than fluoxetine or placebo (15/69, 22%).</p> <p>As the report itself notes, harms from GET, as implied from patient behavior in studies, are significant. I do not know of any scientific study which has measured this in a controlled way, nor do I believe such a study would be ethical. For further reports on harms from GET, please see Reporting of Harms Associated with Graded Exercise Therapy and Cognitive Behavioural Therapy in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, T. Kindlon, Bull. IACFS/ME: 19 (2), Fall 2011. This important paper was omitted from your review because it appeared in a non-indexed journal ("gray literature"). The paper should be evaluated on its merits and its evidence for harms cited in the report. This paper also documents several serious concerns with the methodology used in the PACE trial (see next). Furthermore, it would have been interesting to learn what would have happened if the PACE trial had required participants to repeat the final six-minute walk test one day later – given what we now know about "post-exertional malaise" in patients who have ME, how many would have refused to walk the second day, and what would have been the distances reached for those who did?</p>	We reviewed this paper and it does not meet our inclusion criteria. However, we have expanded our discussion of the limitations of the PACE trial and other studies included for GET.
Charmain Proskauer	Results	<p>p. ES-12 "When combining all studies comparing any type of counseling to no treatment, support, relaxation, or adaptive pacing there is moderate strength of evidence that counseling improves fatigue (8/15 trials showed positive effect)"</p> <p>My question is, if one takes at face value that 8 of 15 studies showed positive effect (and this could be argued in the case of the PACE trial), how does 53% qualify as "moderate"? That would seem to be "low" at best (since 47% of the trials showed no positive effect).</p>	We have taken into consideration the number of patients enrolled in each study, the quality of each study, and the available results, rather than strictly the number of studies - we have clarified this in the table.

Commentator & Affiliation	Section	Comment	Response
Chairman Proskauer	Results	<p>Given the well-documented deficiencies of the PACE trial (granted, the studies documenting the deficiencies were not reviewed in this report), how can the PACE trial be rated as “Good”?</p> <p>In addition to our previous comments/references supporting comments on the deficiencies of the PACE trial (quoted below for convenience) I would draw your attention to the following by Fred Friedberg, PhD, President, International Association for CFS/ME: http://iacfsme.org/PACETrial/tabid/450/Default.aspx IACFS/ME Statement on the PACE Trial: The Issue of Illness "Reversal" February 24, 2011</p> <p>The much publicized UK-based PACE trial (Lancet, Feb. 18th; http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext) reported positive outcomes for patients with CFS/ME who were treated with cognitive-behavior therapy (CBT) or graded exercise therapy (GET) in comparison to a standard medical care condition or an adaptive pacing condition. The adaptive pacing condition was intended to help patients adjust their activity levels according to their available energy (based on envelope theory). The findings were similar to previous CBT and GET studies in CFS. This trial was unique in incorporating a pacing condition and recruiting a very large sample. That said, we have concerns about how the trial was reported.</p> <p>We certainly support any effective treatment for CFS/ME, medical or behavioral. Behavioral interventions are helpful for a number of major medical conditions (cardiovascular disease, diabetes).</p> <p>Illness “Reversal” and Behavioral Intervention</p> <p>The most fundamental concern we have is focused on the type of causal model that was linked to the CBT and GET conditions in this study. The model, based on the application of cognitive-behavioral and physical conditioning principles, predicts that properly designed behavioral or exercise interventions will “reverse” the CFS illness. Not improve symptoms/functioning or provide better management, but “reverse” the illness. This term implies that the illness can be cured (or something close to it) with behavioral techniques.</p> <p>If one assumes such a direct correspondence between behavioral treatment and curative outcomes, then the illness is by implication a psychiatric condition. Once this assumption is made, then research efforts to assemble a biomedical model of CFS are more likely to be delegitimized. And the public’s perception of the illness as simply being tired is again reinforced. Perhaps this is the most unfortunate aspect of the PACE trial: The omission of any reference to the medical complexity of this illness.</p>	<p>Thank you for drawing our attention to the reviews of the PACE trial. The manner of determining study quality (internal validity) is based on specific criteria for study design and implementation. We have judged that the PACE trial remains a good-quality study. The recovery outcome has been added to the report and we have expanded our discussion of the topic of recovery, both in our discussion section and future research section. We have expanded our discussion of the differences that exist between different case definitions but also applaud the investigators of the PACE trial for performing sensitivity analysis with the patients that met the CDC (Reeves, 2003) and London (Sharpe, 1996) case definitions for CFS and ME, respectively, that found similar results. We have highlighted that subgroups of patients with specific symptom sets have not been adequately studied to determine the applicability of these case definitions to these groups.</p>

Commentator & Affiliation	Section	Comment	Response
Chairman Proskauer	Results	<p>Furthermore, when one compares the study goal of illness “reversal” to the reported outcomes, the support for such reversal is modest at best: 30% of GET and CBT patients achieved normative physical functioning-- but the 30% figure was in comparison to 15% who achieved such normative function in the standard medical care control condition.</p> <p>Thus a more accurate statement of this finding would be: An additional 15% of patients in the CBT and GET conditions achieved normal functioning in comparison to standard medical care. The critical standard of clinical significance is that a therapy results in restoration of normal function. But their own data do not support reversal outcomes above and beyond standard medical care for the vast majority of their subjects in the CBT and GET conditions.</p> <p>Question of CFS/ME Diagnosis</p> <p>In addition, the 15% advantage over standard care for patients in CBT and GET can be further questioned given that at least 1/3 of all patients did not meet the strict international criteria for CFS (Table 1 in study)—the diagnostic protocol most often used in published studies. Strict criteria for CFS are linked to poor prognosis and conversely, subjects who don't meet strict criteria for CFS have better outcomes. So the PACE trial folded in a significant number of subjects who do not have CFS according to standard criteria. Again this dilutes the significance of their findings as it makes it more difficult to generalize to the population of people who do have CFS.</p> <p>To put behavioral approaches in context—they can be quite helpful, but they hardly meet the standard of clinical significance that would elevate them to curative interventions. If this had been made clear in the study, it would have provoked far less controversy and debate.</p> <p>Media Mis-reports</p> <p>Finally, the media message from this study has often been: “Exercise is good; Rest is bad.” Although the PACE trial authors did not issue such a statement, I think there is some responsibility to explain to the media that this type of recommendation is simplistic and potentially harmful for patients with CFS/ME. Activity and exercise recommendations must be based on a thorough evaluation and a sensitive individualized approach, not the broad brush that has become the take home message of this study.</p> <p>Fred Friedberg, PhD President IACFS/ME</p>	<p>Thank you for drawing our attention to the reviews of the PACE trial. The manner of determining study quality (internal validity) is based on specific criteria for study design and implementation. We have judged that the PACE trial remains a good-quality study. The recovery outcome has been added to the report and we have expanded our discussion of the topic of recovery, both in our discussion section and future research section. We have expanded our discussion of the differences that exist between different case definitions but also applaud the investigators of the PACE trial for performing sensitivity analysis with the patients that met the CDC (Reeves, 2003) and London (Sharpe, 1996) case definitions for CFS and ME, respectively, that found similar results. We have highlighted that subgroups of patients with specific symptom sets have not been adequately studied to determine the applicability of these case definitions to these groups.</p>

Commentator & Affiliation	Section	Comment	Response
Chairman Proskauer	Results	<p>Extract from our previous comments on the PACE trial 2(d). The Evidence Review failed to examine and report the deficiencies in the PACE trial. The PACE trial featured prominently in this Evidence Review.⁴ It is the largest of all the intervention trials examined, and it reported significant improvement on several outcome measures. However, the Evidence Review failed to examine any of the well-documented deficiencies in this study, which if considered would likely downgrade the Review's assessment of the trial. First, the Evidence Review failed to connect its concerns about the Oxford definition (p. 77) with the subject selection criteria for PACE. The PACE authors used the Oxford definition, and excluded patients "at significant risk of self-harm."⁴</p> <p>While Oxford requires the exclusion of patients with psychosis, bipolar disorder, substance abuse, and organic brain disorder, it does not require the exclusion of patients with depressive or anxiety disorders. Indeed, a subsequent paper reported that 46% of the PACE subjects had anxiety, depression or both.³² Another paper examined the patients enrolled from one PACE center and found that 56% of subjects had a co-morbid psychiatric disorder, including depression, anxiety, obsessive compulsive disorder, post-traumatic stress disorder, and phobias.³³</p> <p>The CBT and GET programs tested in the PACE trial would be predicted to benefit patients with primary psychiatric disorders. Whether the PACE treatments would benefit an ME cohort without co-morbid psychiatric disorders is an important and unresolved question.</p> <p>In addition, the inclusion of patients without ME through the use of the Oxford definition calls into question whether the PACE results can be generalized to ME patients even if they have secondary depression or anxiety. Therefore, the applicability of the PACE results to patients with ME cannot be assumed.</p> <p>Second, PACE relied heavily on self-report outcomes measures, and even discarded the original plan to measure subject activity through actigraphy.³⁴ In a follow-paper, inexplicably excluded from the Evidence Review, the PACE authors acknowledge that objective measures do not correlate well with self-report measures.³⁵</p> <p>The objective measure reported in the PACE trial is the six minute walking test, with the biggest improvement reported in the GET arm of the trial (an increase of 67 meters over baseline 11 to 379 meters).⁴ However, the PACE authors fail to note that this improvement still left the subjects below the 400 meter threshold qualifying for lung transplantation.³⁶</p> <p>The PACE authors have defended the poor results, pointing to variations from how the test is usually performed.³⁷ However, the fact remains that the improvements, even in the GET arm, were not remarkable and not indicative of gain of function.</p>	<p>Thank you for drawing our attention to the reviews of the PACE trial. The manner of determining study quality (internal validity) is based on specific criteria for study design and implementation. We have judged that the PACE trial remains a good-quality study. The recovery outcome has been added to the report and we have expanded our discussion of the topic of recovery, both in our discussion section and future research section. We have expanded our discussion of the differences that exist between different case definitions but also applaud the investigators of the PACE trial for performing sensitivity analysis with the patients that met the CDC (Reeves, 2003) and London (Sharpe, 1996) case definitions for CFS and ME, respectively, that found similar results. We have highlighted that subgroups of patients with specific symptom sets have not been adequately studied to determine the applicability of these case definitions to these groups.</p>

Commentator & Affiliation	Section	Comment	Response
Chairman Proskauer	Results	<p>Third, the follow-up paper on recovery in the PACE trial revealed several post hoc changes to data analysis.³⁵ The most startling is the definition of recovery with an SF-36 physical function score of 60 or less (reduced from the original threshold of 85 or less).³⁴ Given that the entry criteria for PACE included an SF-36 score of 65 or less, this change permits the outcome of patients being classified as “recovered” when in fact their physical function decreased from baseline. This threshold is also notable because the 2005 Reeves Empirical definition uses a diagnostic threshold of 70 or less on the same scale.³⁸</p> <p>Finally, PACE data show that there was a slight increase in the number of participants receiving illness and disability benefits by the end of the trial.³⁹</p> <p>Fourth, the PACE subjects were enrolled based on meeting the Oxford criteria, but were also assessed with the “international criteria” for CFS and the London criteria.⁴ It must be pointed out that the international criteria referenced by the authors was Reeves 2003,⁴⁰ and that the four symptoms required to accompany fatigue were only required to be present for one week.³⁵</p> <p>There is also some controversy over whether the proper London criteria was used.⁴¹ The authors report that 67% of PACE participants met the modified CDC definition, and 51% met the London criteria.³⁵ However, these assessments were made on the Oxford cohort, not independent cohorts, and therefore it is difficult to draw conclusions about patients meeting other case definitions (including correctly applied Fukuda and London).</p> <p>The PACE trial results and subsequent publications have been very controversial. The Evidence Review did not include several of the follow-up papers, and assigned a “Good” quality rating without acknowledging or addressing the many flaws of the PACE trial:</p> <ul style="list-style-type: none"> • PACE used an overly broad definition that could include people with other causes of fatigue; • almost 50% of PACE subjects had psychiatric disorders; • objective measures of physical function showed minor or no improvement; • recovery was redefined in such a way that patients who worsened from baseline could be counted as recovered; and • application of additional diagnostic criteria was flawed. <p>Given these significant flaws, there is a danger of overstating the results of PACE, and certainly a high risk in drawing conclusions about whether PACE is applicable to ME patients. The Evidence Review should reexamine the PACE data, and reconsider its quality assessment.</p> <p>Furthermore, the Evidence Review should interpret the PACE results with caution, particularly the strength of evidence assessments that include PACE.</p>	<p>Thank you for drawing our attention to the reviews of the PACE trial. The manner of determining study quality (internal validity) is based on specific criteria for study design and implementation. We have judged that the PACE trial remains a good-quality study. The recovery outcome has been added to the report and we have expanded our discussion of the topic of recovery, both in our discussion section and future research section. We have expanded our discussion of the differences that exist between different case definitions but also applaud the investigators of the PACE trial for performing sensitivity analysis with the patients that met the CDC (Reeves, 2003) and London (Sharpe, 1996) case definitions for CFS and ME, respectively, that found similar results. We have highlighted that subgroups of patients with specific symptom sets have not been adequately studied to determine the applicability of these case definitions to these groups.</p>
Peer Reviewer #3	Results	<p>The results are meaningless because the inclusion/exclusion process eliminated any useful studies from being included.</p>	<p>Our inclusion criteria were pre-defined and supported by the NIH Working Group prior to initiation of the review.</p>

Commentator & Affiliation	Section	Comment	Response
Tom Kindlon Assistant Chairperson of the Irish ME/CFS Association	Results	The data from this paper, looking at employment outcome measures in the PACE Trial, were not used: PLoS One. 2012;7(8):e40808. doi: 10.1371/journal.pone.0040808. Epub 2012 Aug 1. Adaptive pacing, cognitive behaviour therapy, graded exercise, and specialist medical care for chronic fatigue syndrome: a cost-effectiveness analysis. McCrone P1, Sharpe M, Chalder T, Knapp M, Johnson AL, Goldsmith KA, White PD. http://www.plosone.org/article/info:doi/10.1371/journal.pone.0040808 There are tables with various pieces of data. The authors summarise it as: "There was no clear difference between treatments in terms of lost employment."	This paper is out of scope for this review. We did not review cost-effectiveness.

Commentator & Affiliation	Section	Comment	Response
Tom Kindlon Assistant Chairperson of the Irish ME/CFS Association	Results	<p>Employment data were not reported in the draft ARHQ paper for the following study:</p> <p>O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A. Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme. Health Technol Assess. 2006 Oct;10(37):iii-iv, ix-x, 1-121. http://www.journalslibrary.nihr.ac.uk/hta/volume-10/issue-37</p> <p>"Group CBT did not significantly improve cognitive function, quality of life, *employment status* or healthcare utility measures"</p> <p>"Group CBT did not significantly improve cognitive function, quality of life (as measured by the physical subscale of the SF-36), *employment status* or healthcare utility measures."</p> <p>Details: Baseline pp87 (page 99 of pdf) At 6 months: pp 99 (page 110 of pdf) At 12 months: pp 106 (page 117 of pdf) Some other data from this study: O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A. Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme. Health Technol Assess. 2006 Oct;10(37):iii-iv, ix-x, 1-121. http://www.journalslibrary.nihr.ac.uk/hta/volume-10/issue-37</p> <p>6 minute incremental shuttle walking test: Physical performance – shuttles walked</p> <p>Similar trends were seen with the number of shuttles walked, as was seen for the GHQ scores, with more shuttles walked in the CBT treatment cohort and fewer in the SMC treatment cohort, with the EAS cohort showing results similar to the SMC group. Patients in the CBT cohort completed an average of 22 shuttles (200 m) compared with an average of 19 shuttles in the EAS treatment cohort and 18.3 in the SMC group (Table 7). Again, overall across the three groups the differences were not statistically significant ($p= 0.16$), but the difference between CBT and SMC was nearing statistical significance ($p= 0.060$). On average, patients in the CBT group completed 20% more shuttles than those randomised to SMC (odds ratio 1.20, 95% CI 0.99 to 1.45). As was seen for the other quality of life measures, the mean scores reported at 6 months were similar to those reported at 12 months ($p= 0.80$) and the trend across the groups was unchanged between the 6- and 12-month assessments ($p= 0.99$).</p> <p>Five clear outlying observations were omitted from the analysis of shuttles walked. Three were very low values (0 or 2) and two were amongst the highest values (60 and 75), but were from a patient with a low baseline score (9). If these outliers were retained, the SEs increased and difference between CBT and SMC was no longer statistically significant ($p= 0.17$).</p>	We have added further data on employment outcomes from the O'Dowd, 2006 study

Commentator & Affiliation	Section	Comment	Response
Tom Kindlon Assistant Chairperson of the Irish ME/CFS Association	Results	The number of shuttles walked is illustrated in Figure 3. The distribution was positively skewed in each group, hence median scores are presented. The increase in the median number of shuttles walked in the CBT treatment condition from 20.5 (205 m) at baseline to 30 (300 m) at 12 months suggests an improvement, which did not reach statistical significance. The change from a median of 20.5 shuttles at baseline to 30 shuttles at 12 months in the CBT cohort represents an increase in walking speed at the end of the test from 2.64 to 3.02 miles per hour. The median increase is composed of an additional 4.5 shuttles at 2.64 miles per hour (level 5) and five shuttles at 3.02 miles per hour (level 6). [My comment: I don't believe some or all of the outliers should be excluded. Scores of 60 and 75 are normal scores for healthy people - the paper says: "The ISWT, used as a physical performance measure, has normative reference data described by Taylor and colleagues. Their sample of 122 healthy subjects (mixed gender and age) walked a mean of 67 x10-m shuttles" There is no reason that some people with CFS can't become healthy during a trial. Note that they appear not to have excluded other similar scores as they say "were among the highest" in "two were amongst the highest values (60 and 75)". These scores were only excluded because this person had a low score at baseline. But as I said, there is no reason why somebody couldn't improve during a trial.]	We have added further data on employment outcomes from the O'Dowd, 2006 study.
Tom Kindlon Assistant Chairperson of the Irish ME/CFS Association	Results	The results of a walking test were mentioned for one study but not another: Quote from draft: However, one trial also measured functioning using a walking speed test and found improved walking speed in the CBT group compared with controls (difference from baseline to 12 months for CBT vs. support: 1.77; 95% CI, 0.025 to 3.51; p=0.0055 and difference from baseline to 12 months for CBT vs. no intervention: 2.83; 95% CI, 1.12 to 5.53; p=0.0055).88 88=O'Dowd et al. The following study had a 6-minute walking test and found no difference between CBT and the control group: White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet. 2011;377(9768): 823-36. PMID: 21334061.	These results have been updated in the report.

Commentator & Affiliation	Section	Comment	Response
Tom Kindlon Assistant Chairperson of the Irish ME/CFS Association	Results	<p>Quote from draft: 79. Deale A, Husain K, Chalder T, et al. Long-term outcome of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. <i>Am J Psychiatry</i>. 2001;158(12): 2038-42. PMID: 11729022.</p> <p>Draft has: Three trials reported the number of hours, either per week or per 24-hours, individuals were working, with one trial reporting significantly more hours worked per week for the CBT group compared with relaxation (mean hours of 35.57 vs. 24.00 at 5 years; $p < 0.04$),⁷⁹ Hours worked per week at 5 years was higher in CBT group, mean (SD):35.57 (8.11) vs. 24.00 (4.97); $p < 0.04$ % With full-or part-time employment at 5 year followup: NS Correction: the hours worked figure only apply to a sub-group. See Table 2 of Deale et al. (2001): "Hours worked per week (employed patients only)"</p>	This is noted in the evidence table Appendix G4 in the report.
Tom Kindlon Assistant Chairperson of the Irish ME/CFS Association	Results	<p>I'm dubious about the analysis regarding the harms of diagnosis. This [the harms of diagnosis] should really be compared to being in the same situation without any diagnosis. Instead, I think it combines/conflates two issues: the (i) harms of/problems caused by a diagnosis and (ii) the harms caused/problems caused from simply having the symptoms and impairments.</p> <p>I believe without a diagnosis, it's harder to get support from family/friends/employers/education authorities/disability payers/etc., and it's more likely one will be incorrectly adjudged to be suffering from psychiatric problems. Also, somebody might be more likely to suffer from psychiatric problems (e.g. depression, anxiety, etc.) due to the lack of support of others than if somebody was diagnosed [with ME/CFS].</p> <p>The CDC's 2003 population-based study Reyes M, Nisenbaum R, Hoaglin DC, Unger ER, Emmons C, Randall B, Stewart G, Abbey S, Jones JF, Gantz N, Minden S, Reeves WC. Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas. <i>Archives of Internal Medicine</i> 2003;163:1530-1536 found that a delayed diagnosis was a risk factor for poor prognosis. Woodward, Broom, and Legge found that obtaining a diagnosis was the single most helpful event in the search for social and medical legitimacy during the course of their illness. Woodward RV, Broom DH, Legge DG. Diagnosis in chronic illness: disabling or enabling--the case of chronic fatigue syndrome. <i>J R Soc Med</i>. Jun 1995; 88(6): 325-329.</p>	We agree that patients with ME/CFS have significant symptoms and impairments. Thank you for these references. We have included them in our section about benefits and harms of diagnosis.

Commentator & Affiliation	Section	Comment	Response
Tom Kindlon Assistant Chairperson of the Irish ME/CFS Association	Results	There is a lot of talk of “functioning” (also “function”). I think the report needs to more clearly distinguish between self-reported functioning (which may be biased due to demand characteristics after undergoing therapy) and objective functioning. For example, in the PACE Trial, CBT reported higher physical functioning (as measured by the SF-36 physical function subscale) but no improvement on the 6-minute walking test over (i) APT and (ii) SMC alone.	Thank you for your comment. We have added the 6-minute walking test results from the PACE trial and others as an objective measure of function. The self-reported SF-36 tool has been recognized as a valid measure of function but we have added comments in our future research section as the need for objective measures of change.
Public Reviewer # 51	Results	<p>AHRQ report: Page v. Paragraph on “Results” states: “A diagnosis of ME/CFS is associated with broad psychosocial consequences.” And conclusions on pages vi and 80 state that “GET appears to be associated with harms in some patients whereas the negative effects of being given a diagnosis of ME/CFS appear to be more universal.”</p> <p>Comments: These statements are incorrect and are not supported by the information presented on page 19 regarding the “Key Question 1c- What harms are associated with diagnosing ME/CFS?” They should be deleted or revised. The statements noted above make it appear that being given the diagnosis creates issues for ME/CFS patients. While it is true that most ME/CFS patients do not like the name “Chronic Fatigue Syndrome” and most would prefer that the illness be called “Myalgic Encephalomyelitis”, it is not the diagnosis itself that raises issues. Most patients actually report relief once they have been given a diagnosis for their disabling symptoms. It is the symptoms that lead to disability which in turn impacts employment, ability to attend school and participate in activities of daily living. Also, as correctly stated on page 19 of the Report, prejudices and stereotypes held by healthcare professionals and spread by the media are influenced by the name “Chronic Fatigue Syndrome” as well as treatment recommendations for CBT/GET which imply that ME/CFS is a psychological based disorder versus the biological based disorder that patients know it is.</p>	Thank you for this comment and we have made changes to this section to highlight that although some patients report relief with a diagnosis of ME/CFS, we did not find studies to reflect this patient experience.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #51	Results	<p>The AHRQ report seems to favor studies for CBT and GET and has rated several of them “good” despite many data flaws and difference in case definitions. Meanwhile, studies showing abnormal and sometimes harmful response to exercise are excluded and although the report indicates that it is possible that CBT and GET could be harmful, it does not make that conclusion. I’ve noticed in AHRQ reports on other topics that pharmacological studies sponsored by pharmaceutical companies are often faulted for potential bias, yet behavioral based intervention studies conducted by mental health clinicians, whose livelihood depends on providing these treatments, are not criticized as being biased. The Report should be amended to mention the potential bias related to counseling and behavioral therapies.</p> <p>The PACE trial (White, et al., 2011) 98, is one of the few treatment trials to receive a “good” rating, and it is froth with methodological issues. The issues include:</p> <ol style="list-style-type: none"> 1. The PACE trial used the Oxford definition, which the AHRQ report notes can be problematic in that it included people with idiopathic fatigue and primary depression who most likely do not have ME/CFS. 2. Patient performance on the “6-minute walking test” at the end of the trial showed no significant improvement and results are indicative of continued severe functional impairment on the level of someone with heart failure. For an comprehensive analysis of this component of the PACE study, I recommend this article by Susanna Agardy (Australia), “Recovery’ in PACE, the 6 Minute Walking Test and Other Issues: How Well Can ‘Recovered’ Patients Walk?” 3. Due to changes in the methodology after the conclusion of the study someone could enter the trial with a SF-36 physical function score of 65 and end with a score of 60 and be considered “recovered”. So people who scored lower after the intervention was completed were considered to be cured, huh? Putting methodology issues aside, it should also be noted that an SF-36 score of 60 would be comparable to someone with early stage heart failure, and since the average age of the participants in the study was 39 years, that alone should be raising red flags. A subsequent publication using the PACE data called “Recovery from chronic fatigue syndrome after treatments given in the PACE trial” published by the authors of the PACE trial in Psychol Med in October 2013 (43(10): 2227–2235), acknowledges the post-hoc methodology changes in the study. Oddly, this paper is not even mentioned in the AHRQ report. The above points should cause significant concern over the methods and analysis used in this study. 	<p>The quality rating (internal validity) of trials is a multi-step process and although the trial may be rated as good, that is not to say that the differences in case definitions may limit the interpretation of the data to subgroups. We have expanded our discussion regarding the limitations and applicability of these studies. We have added the 6 MWT and expanded the results and discussion to report on the outcome of recovery and its limitations</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 51	Results	In summary, the PACE trial has been one of the most disputed trials in ME/CFS research history. Much of these disputes can be found in the form of letters to the editors and other published articles that were not included in the AHRQ search. Freedom of information requests asking for the raw data from the trial to be made available for outside analysis have been repeatedly denied. Some speculate that PACE, one of the few ME/CFS studies to receive significant funding by the UK government, was performed with an ulterior motive of the NHS to limit health coverage and access to disability benefits for ME/CFS patients in the United Kingdom. There is acknowledgement of conflicts of interest of several of the studies investigators in the published study that could help to substantiate that claim and there is obvious bias by the researchers who have a financial interest in promoting behavioral interventions Because of the definition, methodological issues, biases and conflicts of interest, the overall rating for the PACE study should be downgraded from good to poor, or better yet this study should be excluded from the analysis.	The quality rating (internal validity) of trials is a multi-step process and although the trial may be rated as good, that is not to say that the differences in case definitions may limit the interpretation of the data to subgroups. We have expanded our discussion regarding the limitations and applicability of these studies. We have added the 6 MWT and expanded the results and discussion to report on the outcome of recovery and its limitations.
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Results	The Review misinterprets some of the papers expressing harms associated with a diagnosis. The Review fails to acknowledge the relief and value of finally getting a diagnosis, particularly from a competent and supportive physician. The harm is not from receiving the diagnostic label, but rather from the all too common delay in diagnosis and the subsequent response from incompetent healthcare providers. At the same time, the Review failed to acknowledge the severe harm that patients face if they are given harmful treatments based on the mistaken belief that ME/CFS isn't a real biological illness, but a psychological or behavioral problem.	Thank you for your comments. We have expanded our discussion of the harms/benefits of receiving a diagnosis of ME/CFS as well as highlighted the lack of subgroup analysis in the treatment trials. We have also expanded our discussion of the applicability of the results particularly in light of the fact that the most severely affected patients, those bedridden for example, have not been eligible to participate in these trials. Additionally, outcomes measured often did not report harms adequately. We have identified this in our report as an area for future research to address.

Commentator & Affiliation	Section	Comment	Response
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Results	<ul style="list-style-type: none"> Conclusions about treatment effects and harms failed to consider what is known biologically about ME and its likely response to the therapies being recommended. This means that the PACE (an Oxford study) results for CBT and GET were not only accepted (despite the many flaws in those data), but were determined to be broadly applicable to people meeting any of the case definitions. Data on the abnormal physiological response to exercise in ME patients were excluded, and so the Review did not conclude that CBT and GET could be harmful to these patients (although it did allow it might be possible). The Review claims that its findings are applicable to all patients meeting any CFS or ME definition, regardless of the case definition used in a particular study. Seeing how disparate the patient populations and their physiological pathologies are between the definitions, this is obviously a false and unfounded assumption, and simply not the case in the real world and clinical settings. 	We have attempted to provide a brief background to the illness in the introduction but delving into the etiology and pathophysiology was beyond the scope of this report. We have expanded our discussion of the limitations, applicability (including a lack of subgroup analysis) and needs for future research. Additionally, we have further highlighted the studies based on their case definitions for more transparent comparison.
Public Reviewer # 7	Results	The Draft Report states that: "The PACE Trial described previously was a large 12-month good quality trial (n=641) comparing four interventions: CBT; GET; an adaptive pacing therapy; and a usual care control group.[98] Attrition was low with only 1.7 percent withdrawing overall and adherence was not reported." However, when reading the 2011 Lancet paper (see below URL) there appears to be 53/641 (8.3%) formal withdrawals and an additional 32/641 (5.0%) lost to followup. It is unclear how the figure of 1.7% was calculated. http://www.thelancet.com/journals/lancet/article/PIIS0140673611600962/images?imgId=gr1&sectionType=red	This data has been reviewed, and the results have been modified accordingly.
Solve ME/CFS Initiative and Research Advisory Council	Results	Incorrect citation for the study at the bottom of page 19, "Specifically, 21 patients had been given a psychiatric diagnosis when one did not exist, and 13 patients who had never been given a psychiatric diagnosis actually had a treatable psychiatric condition in addition to CFS.52" Please note we do not know what the correct citation is, only that citation 52 is not correct.	This citation has been changed.
Solve ME/CFS Initiative and Research Advisory Council	Results	On page 22 under Medications, even though rintatolimod is not FDA approved, at one time it was approved (and it still may be approved) for compassionate use. If this is true, this should be added to this section.	We were not able to find evidence that rintatolimod is currently approved even for compassionate use.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 40	Results	<p>...The PACE Trial, alas, did not go as planned. The Protocol specified outcomes of improvement for patients receiving CBT and GET that involved significant increase in levels of activity. As the trial proceeded it became obvious to the trial supervisor that the desired improvements were not happening. Rather than lose the game the supervisor moved the goal posts. Activity meters had been meant to be worn by trial participants afterwards to measure objectively the increases in activity the trial's authors expected. Suddenly it was decided that wearing the watch-like instruments would be too exhausting for these individuals, however supposedly strengthened by CBT and GET. And the number chosen as the cut-off for measuring improved status with a questionnaire was lowered by more than 25% -- from 85 to 65. Actually, 65 had been the mark for patients considered unwell enough to enter the trial to begin with. So a person could start off unwell and end up unwell and yet be pronounced recovered, thanks to the wonders of statistics. ...</p>	<p>Thank you for your thoughtful review of the PACE study. We have expanded our reporting of the findings, including the updated harms data, and have also expanded our critical appraisal of this study in the discussion, limitations, and applicability section.</p>
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Results	<p>Severe well-known quality issues with individual studies were either not considered or ignored. The PACE trial in particular; the Review failed to examine any of the well-documented deficiencies in this study, which if considered would likely downgrade the Review's assessment of the trial.</p>	<p>We have expanded the presentation to include a more thorough critical appraisal of the PACE trial and expanded our discussion of the limitations and applicability.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2	Results	<p>Where results from subjective and objective outcome measures diverge it is no more reasonable for researchers to decide amongst themselves that biopsychosocial interventions tested in non-blinded trials should be assessed primarily via subjective self-report measures than it would be if they were testing Chakra balancing healing or anything else. It is important that claims about the efficacy of treatments are based upon good and reliable evidence, or else those with health problems can find themselves losing their lives to health interventions whose efficacy has been misrepresented to them. I do not believe that most patients would see an intervention which allowed them to fill in questionnaires more positively, but not actually perform any more activity, to be genuinely effective. It seems that the developers of CBT for CFS formerly agreed. Biopsychosocial rehabilitative approaches take considerable time and effort, and whenever claims about their efficacy are based upon non-blinded trials and subjective self-report measures it is important the the potential problems with response bias are clearly explained. When discussing the evidence that CBT and GET improve symptoms on page 76 (122 of pdf) the only reference to the problems with self-reporting relate to adherence. In order to use the available evidence to claim that CBT and GET improve patient's symptoms, one first need to provide good evidence that the questionnaires used in these non-blinded trials are reliable measures of patient's symptoms (which the review recognises has not been done) - without this, it should only be claimed that CBT and GET can lead to patients describing their symptoms more positively on questionnaires.</p>	<p>Thank you for your comments - we agree that objective measures are optimal but in their absence, reporting on subjective experience may provide insight into the effectiveness and areas for future research. As indicated in our report, decreased fatigue outcomes of CBT and GET were considered low strength of evidence; low strength of evidence indicates that further research is likely to change the impression and conclusions. We have expanded our limitations section and discussion on the biases noted within these studies, including "response bias."</p>
Public Reviewer #2	Results	<p>While I have not been able to look closely at this, I am also concerned that the draft review seems to make exaggerated claims about the value of CBT for improving employment. The PACE trial was reported in the review as showing improvement, yet in one of the PACE trial's papers they reported that "there was no clear difference between treatments in terms of lost employment", and "receipt of benefits due to illness or disability increased slightly from baseline to follow-up" [11]. It cannot be right to assess employment outcomes via WSAS scores rather than the measured employment outcomes.</p>	<p>We have expanded our discussion of the limitations of the work and social adjustment scale for measuring employment outcomes. However, this was not the only included measure for employment status.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2	Results	<p>Also, while this report is in French, a review of Belgium CFS clinic providing biopsychosocial rehabilitative approaches is available here: http://www.inami.fgov.be/care/fr/revalidatie/general-information/studies/study-sfc-cvs/index.htm As well as providing information on the efficacy of these interventions in a setting outside of medical trials, this assessment also has the advantage of having been conducted by those without a vested interest in making positive claims about the value of CBT/GET. This report again finds that the interventions assessed did not lead to improvements in employment outcomes. Results from the CFS/ME National Outcomes Database have also been published [12], this time by those involved in running the centers assessed. Results showed that centres providing CBT/GET seemed to perform less well than those providing just 'activity management', and with all performing less well on the self-report measures used than we saw in the recently reported PACE trial [8,13].</p> <p>We are currently lacking good evidence that biopsychosocial rehabilitative approaches are more effective than placebo, Chakra healing, or any other intervention that leaves patients wanting to be positive to their therapist and that is assessed via self-report measures. It is important that this is made clear so that patients are able to make informed decisions about their own medical care and their own lives.</p>	<p>We did not include foreign language literature in this report. We have expanded our discussion of the limitations of the current treatments.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #8	Results	<p>There is considerable concern from patients that one of the side-effects of the medicalisation of the psychosocial aspects of ME/CFS patient's lives is that some medical staff see this as an excuse to take it upon themselves to manipulate patients as they see fit, without informed consent. There does seem to be a problem with unduly positive claims made about the efficacy of treatments and the likelihood of recovery, with this leading to understandable anger and distrust. I think that aspects of these problems can be seen in two biopsychosocial trials that the draft review has assessed as being of good quality. In the FINE trial [14] patients were encouraged to adopt a range of positive cognitions, this involved 'Rousing Reassurance' such as:</p> <p>From the moment you walk out of this room your recovery is beginning. There is no disease Go for 100% recovery. [15]</p> <p>Unsupported claims were made about the reversible nature of patient's condition were made to patients and medical staff. While the treatment itself was shown to be ineffective, even at improving patient's questionnaire scores, unsurprisingly the cognitions promoted still had an impact, and led to further unreasonable assumptions being made. The views of some specially trained nurses was summed up (in a paper which seemed unconcerned by the ineffective nature of the treatment being provided) with the quote: "The bastards don't want to get better". [16]</p> <p>Despite the poor results of the FINE trial, and the prejudices promoted by the nature of the intervention, Alison Weardon still describes her involvement in this trial and the development this treatment for CFS as being the proudest moment of her career.[17] I believe that this help illustrate a problem with ideological and emotional conflicts of interest that are commonplace in ME/CFS research. A recent Cochrane editorial reported what should be "a cardinal rule: the need to separate the clinical evaluation of innovations from their innovators, who irrespective of any of their endeavors to be 'neutral' have a substantial investment, whether emotional, perhaps financial, or in terms of professional or international status, in the successful implementation of their idea." [18] Some attempt should be made to distinguish between, and compare results from, those trials carried out by those previously unattached to the treatments being assessed, and those whose careers have been focused upon the development of the involved treatments.</p>	<p>Thank you for your comments - we have expanded our discussion of the FINE and PACE trials including their limitations and how they contribute to our current understanding of benefits and harms of treatments. Quality rating (internal validity) of a trial is a multi-step process and the investigators still consider it a well-conducted study despite the limitations surrounding the outcome measures.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #8	Results	<p>After the FINE trial released results in the manner laid out in it's protocol and reported a null result, it's sister trial PACE [8] published and interpreted results in ways which seriously deviated from it's own protocol [13]. The abandonment of the 'positive outcome' criteria, a primary outcome, served to make it far easier for researchers to claim the treatments assessed were of clinical value, but the area where there has been the most concern has been related to claims about 'recovery' - clearly an emotional matter for patients who are so desperate to get better, but also have to endure the sort of prejudices seen above.</p> <p>The PACE trial's published protocol [13] defined 'recovery' as requiring an SF-36 Physical Functioning (SF36-PF) questionnaire score of at least 85 out of 100, while the trial's entry criteria required a score of 65 or under, which was taken to indicate that patients' fatigue was disabling. The post-hoc criteria for recovery allowed patients with an SF36-PF score of 60 to be classed as recovered. This change was justified by the claim that a threshold of 85 would mean "approximately half the general working age population would fall outside the normal range." [19] In fact, the data cited showed that the median score for the working age population was 100, less than 18% of the general working age population had a score under 85, and 15% had declared a long-term health problem [20,21].</p> <p>An SF36-PF score of 60 was claimed in the Lancet PACE paper to be the mean -1sd of the working age population, and thus a suitable threshold for 'normal' disability [8]. They had in fact used data which included all those aged over 65, reducing the mean physical function score and increasing the SD [20]. For the working age population the mean -1sd was over 70, requiring patients to score at least 75 to fall within this 'normal range' [21]. Also, the trial's protocol makes it clear that the thresholds for recovery (including ≥ 85 for SF-36 PF) were intended to be more demanding than those for the mean -1sd, reporting that: "A score of 70 is about one standard deviation below the mean... for the UK adult population" [13]. Patients could be classed as recovered when reporting no change, or even a decline, in either of the trial's primary outcomes.</p> <p>Even using the loose post-hoc criteria for recovery, only 22% of patients were classed as recovered following treatment with specialist medical care and additional CBT or GET [19]. Regardless, the BMJ had reported that PACE showed CBT and GET "cured" 30% and 28% of patients respectively [22], a Lancet commentary which had been reviewed by the PACE trial's researchers claimed that about 30% recovered using a "strict criterion" for recovery [23], and a paper aimed at NHS commissioners stated PACE indicated a recovery rate of 30-40% for CBT and GET [24,25]. It is not surprising that such misstatements of fact will cause problems for patients, promote unwarranted assumptions and prejudices, and lead to a culture of distrust.</p>	<p>Thank you for your comments - we have expanded our discussion of the FINE and PACE trials including their limitations and how they contribute to our current understanding of benefits and harms of treatments. Quality rating (internal validity) of a trial is a multi-step process and the investigators still consider it a well-conducted study despite the limitations surrounding the outcome measures.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #8	Results	<p>While patient's expectations for treatments were recorded before treatments in PACE began, and this showed greater expected gain for APT than CBT and GET, this should not reassure us that improvements in self-reported outcome measures were not a result of bias. The therapists and participants manuals for CBT and GET all include positive claims about the efficacy of the treatment being assessed which would be likely to affect patient's expectations, and equivalent claims were not made to those receiving APT, eg: "In previous research studies, most people with CFS/ME felt either 'much better' or 'very much better' with GET." [GET participant manual, p28][26] More generally, there should be concern that any biopsychosocial intervention intending to alter patient cognitions or understanding of themselves is likely to lead to problems with bias on self-report measures. The description of CBT used in the 2001 Lancet study [4] makes it clear that challenging the patient's view of themselves as a patient is a core part of the intervention [27]. Any analysis of outcome data should be done with an awareness of the danger that patients may then try to describe their health more positively, despite not having seen any real improvement in health. Considering the problems detailed above, and your own criteria, it is surprising that the PACE trial was classed as being of good quality.</p>	<p>Thank you for your comments - we have expanded our discussion of the FINE and PACE trials including their limitations and how they contribute to our current understanding of benefits and harms of treatments. Quality rating (internal validity) of a trial is a multi-step process and the investigators still consider it a well-conducted study despite the limitations surrounding the outcome measures.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #9	Results	<p>Unfortunately, I do not think that I have time to properly raise important matters about the social context in which biopsychosocial approaches need to be assessed (I know that you wanted another five pages of this). In the draft report's assessment of potential harms related to diagnosis, I do not think that this was done well, and seemed to slip into presenting the harms of illness as being overly related to diagnosis, as well as failing to think seriously about why certain unreasonable prejudices can affect medical staff and harm patients. I think that the above example from the FINE trial, and wider concerns about the exaggerated claims made for the benefits of biopsychosocial approaches should be considered. Also - surely you can just use your imagination and recognise: "Chronic Fatigue Syndrome: if you're seriously disabled with that people are going to make fun of you". It's difficult to imagine anyone coming up with a name like that, or 'chronic multisymptom illness' or 'feel too poorly disease' without realising that it will lead to patients facing derision.</p> <p>One important point relating to the harms of diagnosis, is the potential financial cost of a diagnosis of CFS over ME. In a talk Peter White gave to Swiss Re Insurers he explained that a diagnosis of CFS can fall under an insurance policies mental health exclusion: "The point made is that a diagnosis of Myalgic Encephalomyelitis or ME (a term often used colloquially instead of CFS) is considered a neurological condition according to the arrangement of the International Classification of Diseases (ICD) diagnostic codes whereas CFS can alternatively be defined as neurasthenia which is in the mental health chapter of ICD10." [28] Some important stakeholders have a clear interest in ME/CFS patients being given a diagnosis which allows them to be classed as mentally ill, or that their ill health is a result of a refusal to think and behave as they should. The PACE trial's three Primary Investigators all reported conflicts of interest involving the insurance industry. [8]</p> <p>There has also been considerable concern from a range of disability campaigners about the way the biopsychosocial model has been used by the insurance industry and UK government to undermine the interests of the sick and disabled [29-33]. Allowing a group of researchers and medical staff to claim authority over how patients diagnosed with a condition like ME/CFS should think and behave has clear political and moral implications, and too often, matters in this area are decided within processes that give little real power to patients themselves.</p>	<p>Thank you for your comment - we recognize the devastating effects that ME/CFS have on patients and have attempted to discuss the harms of diagnosis based on scientific evidence rather than strictly opinion pieces and case experience, without negating individual's experience. We did follow a pre-defined systematic method in order to minimize any risk that we ourselves might inaccurately represent the science that may occur if we included non-comparative studies.</p> <p>Commenting on the way the insurance industry or government agencies make decisions is beyond the scope of this report and our expertise.</p>

Commentator & Affiliation	Section	Comment	Response
Kartik A. Parekh	Results	<p>AHRQ has critically erred in assuming that CDC and other CFS case definitions have demonstrated sufficient sensitivity and specificity to capture the disease entity Myalgic Encephalomyelitis (ME), as well as similar entities observed in cluster outbreaks in the US in the 1980's which prompted CDC involvement and, ultimately, the creation of the CFS construct. Until this can be demonstrated, CFS definitions cannot be said to have been validated or necessarily relevant for those cases or, indeed, for any patients who meet extant criteria for ME, an entity that was clinically observed in epidemic and sporadic cases studied by Ramsay and others, recognized by WHO, and clinically defined years before the CDC's Holmes committee created the first CFS case definition. Further, as can be inferred from comparative analyses of their respective case definitions, and by the fact that there are patients who meet ME but not CFS criteria, ME cannot be classified as a subset of CFS.</p> <p>AHRQ has failed to consider that CFS case definitions, and the patient groups they select, only overlap those of ME, rather than encompassing them. This is clearly illustrated by the fact that there is no single necessary criterion shared both by extant ME and CFS case definitions except disease chronicity. [1-5]† Thus the AHRQ report's relegation of ME to a 'subset' of CFS has no sound logical or scientific foundation, and neither does its recommendation for a single all-encompassing ME/CFS definition.</p>	<p>Thank you for your analysis. We appreciate that the case definitions are very different and that some are more inclusive than others and may reflect less severe cases or non-cases of ME/CFS as is fully outlined in the Key Question 1 response of the report. After consultation with our working group and Technical Expert Panel, we did elect to include all case definitions in the report a priori for several reasons. First, there are very few trials and excluding some of these definitions would limit the evidence even further than is already outlined. Second, the intent was that this could at least provide a foundation to determine what interventions may be effective. Where available, we compared findings using different case definitions to determine if findings were consistent or not across studies. We have expanded the research needs discussion to indicate that future studies should perform sensitivity analysis to determine differences between case definitions as well as subgroups of patients that meet different criteria. We have elected to use the term ME/CFS at the outset of the report in order to not risk missing important and/or informative evidence that may be labeled under one term or another. By using this term throughout the report, we are not endorsing or refuting that these labels reflect the same disease state. We are hopeful that the evidence reported under research question one will help to shed light on this controversial topic for the P2P workshop.</p>

Commentator & Affiliation	Section	Comment	Response
Kartik A. Parekh	Results	<p>AHRQ has critically erred in assuming that CDC and other CFS case definitions have demonstrated sufficient sensitivity and specificity to capture the disease entity Myalgic Encephalomyelitis (ME), as well as similar entities observed in cluster outbreaks in the US in the 1980's which prompted CDC involvement and, ultimately, the creation of the CFS construct. Until this can be demonstrated, CFS definitions cannot be said to have been validated or necessarily relevant for those cases or, indeed, for any patients who meet extant criteria for ME, an entity that was clinically observed in epidemic and sporadic cases studied by Ramsay and others, recognized by WHO, and clinically defined years before the CDC's Holmes committee created the first CFS case definition. Further, as can be inferred from comparative analyses of their respective case definitions, and by the fact that there are patients who meet ME but not CFS criteria, ME cannot be classified as a subset of CFS.</p> <p>AHRQ has failed to consider that CFS case definitions, and the patient groups they select, only overlap those of ME, rather than encompassing them. This is clearly illustrated by the fact that there is no single necessary criterion shared both by extant ME and CFS case definitions except disease chronicity. [1-5]† Thus the AHRQ report's relegation of ME to a 'subset' of CFS has no sound logical or scientific foundation, and neither does its recommendation for a single all-encompassing ME/CFS definition.</p>	<p>We have edited our report to highlight any differences noted when different case definitions are used. It was our intent to err on the side of including important and/or informative evidence from earlier studies and to also highlight differences if differences exist.</p>
Public Reviewer # 38	Results	<p>The evidence presented in the body of the report about GET is contradictory, yet the conclusion in the abstract suggests that GET is helpful. Here are some quotes from the report.</p> <p>Page 21: "Graded exercise treatment (GET) was superior to control groups in measures of fatigue (low strength), function (moderate strength), and clinical global impression of change (moderate strength) based on one-good quality and three fair-quality randomized trials."</p> <p>Page 46: "There is low strength of evidence that exercise therapy was superior to control groups in measures of fatigue, function, and clinical impression of change."</p> <p>Page 49 and page 76: "In summary, GET improves function (moderate strength), and global improvement (moderate strength), and fatigue (low strength) in ME/CFS patients compared with control groups."</p> <p>Page 76: "Several previous studies have found worsening effects with exercise" Of the 4 exercise trials summarized in Figure 4 (changes in CGI scale) and Figure 5 (changes in SF-36 scale), three use the Oxford criteria -- Fulcher and White (1997) and two by White et al. (2011) (PACE Trials). This report acknowledges issues with the Oxford criteria, so it is surprising that the conclusion in the abstract relies so heavily on these studies. Please revise the abstract and executive summary to reflect the actual evidence in the report.</p>	<p>Thank you for your comment. We have expanded the presentation including a more thorough critical appraisal of these studies and expanded our discussion of the limitations and applicability given the different case definitions.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 38	Results	<p>Typos: Page 46: "serious hars" should read "serious harms"</p>	This has been corrected.
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Results	<ul style="list-style-type: none"> • Counseling and CBT treatment trials were inappropriately pooled without regard for the vast differences in therapeutic intent across these trials. This meant that CBT treatments aimed at "correcting false illness beliefs" were lumped together with pacing and supportive counseling studies, and treated as equivalent. 	We have run sensitivity analyses removing studies that were not of CBT vs. a control; we included this information in the results.
Public Reviewer # 42	Results	<p>Page ES12 this paragraph doesnt make sense. When combining all studies comparing any type of counseling to no treatment support relaxation or adaptive pacing there is moderate strength of evidence that counseling improves fatigue 815 trials showed positive effect and global improvement and global improvement 33 trials showed positive effect It is hard to understand that there was a trial comparing counselling against the other complex set of criteria. In addition global improvement seems to be repeated. And the word decreased is missed out so it appears work impairment is improved rather than decreased work impairment. The study information in brackets does not help clarity.</p>	Thank you - we have made edits to the executive summary and clarified this section.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #41	Results	<p>TEST 1 CardioPulmonary Exercise Testing with measurement of VO2 max anaerobic threshold and maximal heart rate and respiration. This test is mentioned in the book Disability and CFS Clinical Legal and Patient Perspectives with this comment by Dr. Daniel Peterson One objective and reproducible technique for determining and measuring functional disability that should be used consistently is CardioPulmonary Exercise Testing with measurement of VO2 max anaerobic threshold and maximal heart rate and respiration. The test is well established sedentary and ill norms are published and the technology is relatively inexpensive and quite available. Approximately 1700 patients as in 1997 have been tested over the past 10 years and the test is now used on the initial visit to screen patients to direct rehabilitation and adjunctively to determine disability. Diminished Cardiopulmonary Capacity During Post Exertional Malaise Abstract J. Mark VanNess PhD Christopher R. Snell PhD Staci R. Stevens Conclusion In the absence of a second exercise test the lack of any significant differences for the first test would appear to suggest no functional impairment in CFS patients. However the results from the second test indicate the presence of a CFS related postexertional malaise. It might be concluded then that a single exercise test is insufficient to demonstrate functional impairment in CFS patients. A second test may be necessary to document the atypical recovery response and protracted malaise unique to CFS. Legal and Scientific Considerations of the Exercise Stress Test Ciccolla Stevens Snell Van Ness 2007 The Haworth Press This article examines the legal and scientific basis on which an exercise stress test can provide medically acceptable evidence of disability for the CFS patient. This research group's excellent work proves the postexertional disability that ME CFS patients suffer much worse on average than heart failure and COPD patients.</p> <p>TEST 2 Brain neuro SPECT PET scans and MRI brain scan Evidence From 2007 IACFSM. E. conference New methods in viral studies using refined technology show further abnormalities in subsets of MECFS patients. Increased use of instruments like MRI SPECTSPET PET and fMRI show some of the abnormalities in functioning that patients with MECFS experience on a daily basis but these may not have practical application if a patient cannot have this testing done. A number of abnormalities with reduced responsiveness on fMRI is an essential feature of MECFS. Brain imaging shows that amongst other abnormalities MECFS patients have reduced blood flow to the brain especially to areas that are involved in autonomic nervous system functioning and in sleep concentration and pain including the prefrontal cortices the anterior cingulate and the cerebellum altered patterns of brain activation reduced grey matter volume altered serotonergic neurotransmission and reduced acetylcarnitine uptake.</p>	<p>Thank you - when VO2 max anaerobic threshold was used as a functional outcome, it was reported in this review. Otherwise, reporting of intermediate outcomes, including imaging studies and biomarkers, was beyond the scope of this review.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #41	Results	<p>A collaboration of researchers from Spain Belgium and Australia used SPET scanning to observe patterns of brain activity they found that the brain abnormalities correlated with abnormal immune results. Patients with MECFS require more brain regions to perform tasks i.e. they have to work harder to achieve the same results as healthy controls. One particular area of the brain the Wernicke area essential for understanding and formulating coherent speech showed evidence of reduced activity after exercise. Proton resonance spectroscopy showed greatly increased levels of brain metabolites lactate levels were 300 higher than in controls. According to Dr Tae Park from South Korea the unexplained bright spots on MRI scans of some MECFS patients are evidence of an arteriolar vasculopathy or a blood vessel disease. He believes MECFS is a systemic microvascular inflammatory process a process that would affect not only the brain or the heart or the muscles but potentially every organ system in the body. Dr Park found not only capillary inflammation and perivascular cuffing the accumulation of immune cells that surround injured blood vessels but that all the MECFS patients in his study demonstrated remarkably reduced renal blood flow. Dr Park noted that diabetics with renal vascular disease also complain of profound fatigue. Dr Hiro Kuratsune from Japan gave a summary of what is known about brain function in MECFS. It has been known for over a decade that frontal and temporal lobe blood flow is reduced in MECFS and that exercise exacerbates this reduced blood flow for up to 72 hours. The new evidence is that elevated elastase and RNaseL levels correlate with reduced blood flow. It is known that the MRI is abnormal in the majority of people with MECFS due to numerous T2 weighted hypertense foci with evidence of demyelination. Patients with more brain abnormalities tend to be more physically impaired. The remarkable similarity in the brain images of patients with MECFS and multiple sclerosis was noted. Dr Gudrun Lange from New Jersey USA stated what can be said with certainty about the central nervous system findings in MECFS1 the major cognitive problem seen is in information processing2 studies showing reduced cerebral blood flow are starting to show consistency3 there is a problem with serotonergic neurotransmission in the hippocampus and anterior cingulate regions4 there are spinal fluid abnormalities5 fMRI studies are showing altered patterns of brain activation. See references at the end of this article for more Neuroimaging evidence for MECFS diagnosis. TEST 3 Mitochondrial Dysfunction The magnetic resonance spectroscopy MRS brain scan is a most informative of the brain scans for MECFS. It indicates mitochondrial dysfunction. Check www.cocure.com in the archives for more info on MRS and google Dr Cheneys MRS scan data for his patients. MRS scanning has found abnormally high lactic acid spikes near around the hippocampus in PWME brains which indicates mitochondrial dysfunction a central feature being found in just about all cases through the UKs BioLab testing</p>	<p>Thank you - when VO2 max anaerobic threshold was used as a functional outcome, it was reported in this review. Otherwise, reporting of intermediate outcomes, including imaging studies and biomarkers, was beyond the scope of this review.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 41	Results	<p>An MRI is good for ruling out gross abnormalities such as tumors and obvious areas of brain damage while the SPECT can help verify hypoperfusion in the brain. From 2007 IACFSM. E. Conferencer Jonathan Kerr from London stated that his gene expression studies are finding three main abnormalities in MECFS patients these involve the immune system mitochondrial function and Gprotein signaling. There are seven genes upregulated in MECFS those associated with apoptosis pesticides mitochondria function demyelination and viral binding sites. Kerr mentioned three genes in particular gelsolin which is involved in apoptosis and amyloidosis one that is upregulated by organophosphates and a mitochondrial gene involved in the demyelination of nerves. Also Mitochondrial abnormalities in the postviral fatigue syndrome. Behan WM More IA Behan PO Department of Pathology University of Glasgow Scotland. Acta Neuropathol 1991831615 We have examined the muscle biopsies of 50 patients who had postviral fatigue syndrome PFS for from 1 to 17 years. We found mild to severe atrophy of type II fibres in 39 biopsies with a mild to moderate excess of lipid. On ultrastructural examination 35 of these specimens showed branching and fusion of mitochondrial cristae. Mitochondrial degeneration was obvious in 40 of the biopsies with swelling vacuolation myelin figures and secondary lysosomes. These abnormalities were in obvious contrast to control biopsies where even mild changes were rarely detected. The findings described here provide the first evidence that PFS may be due to a mitochondrial disorder precipitated by a virus infection. TEST 4 TH1TH2 imbalance TH1TH2 Cytokine Production Immune testing availability http://punevx.com Th1Th2 Imbalance There are two general branches Th1Th2 of the immune system. Some patients appear to have an over activation of the anti-inflammatory Th2 branch and an under activation of the pro-inflammatory Th1 branch of the immune system</p>	<p>Thank you - when VO2 max anaerobic threshold was used as a functional outcome, it was reported in this review. Otherwise, reporting of intermediate outcomes, including imaging studies and biomarkers, was beyond the scope of this review.</p>
Public Reviewer # 43	Results	<p>I have been ill for 28 yrs. When I was 24 years old and working as a word processor in a downtown Denver law firm I contracted a virus that shut down my immune system and my energy system at the cellular level in the mitochondria. There is research out there to PROVE what I am telling you is CORRECT. Please please please read the above articles and get informed on this most serious debilitating understudied and underfunded illness that has taken my quality of life away and also the lives of many other people. I personally know six patients that have committed suicide because they have lost hope from being so ill with no medical help. I don't mean they don't have doctors I mean that the doctors' hands are tied to help because there are NO TREATMENTS available for this sick population. How would you like to be a doctor that cannot help his ill patients? If you can't put yourself in MY shoes please put yourself in the shoes of any doctor in America that is currently unable to help their patients because of the misinformed undereducated people on the IOM committee who are making decisions that affect us all.</p>	<p>Thank you for sharing your story. Unfortunately, the articles you have recommended do not meet the inclusion criteria for this report. This review focuses on the diagnosis and treatment of the syndrome of ME/CFS and is not all inclusive of the field of study for ME/CFS.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 43	Results	The PACE trial results on CBT and GET were given excessive consideration and too much influence in results of your data review. I personally received this therapy and it caused me to lose considerable functioning that I was never able to regain.	Thank you for your comments. We have discussed the limitations of this study as well as others more comprehensively.
Public Reviewer # 46	Results	The failure to be clear and specific about what disease was being studied. The acceptance of 8 disparate ME or CFS definitions as equivalent in spite of dramatic differences in inclusion and exclusion criteria. The bad science reflected in citing Oxford's flaws and then using Oxford studies anyway. The well-known problems with the PACE trial. The flawed process that used nonexperts on such a controversial and conflicted area. Flawed search methods that focused on fatigue. Outright errors in some of the basic information in the report and apparent inconsistencies in how inclusion criteria were applied. Poorly designed and imprecise review questions. Misinterpretation of cited literature.	Thank you for your comments. Please see above regarding the decision to include all case definitions. Please also note that we reworded our inclusion criteria for Key Question 1 to better reflect that we only included studies of fatigue wherein the diagnosis of ME/CFS was a consideration.
TEP Reviewer #2	Discussion	Future research section points to important work that needs to be done on better delineating the case definition and conducting more rigorous intervention trials with a single case definition.	We agree.
TEP Reviewer #2	Discussion	Of course, given the low level of publishing in this field and the absence of more focused funding mechanisms (e.g., RFA), these are long range goals.	We agree but are hopeful.
TEP Reviewer #3	Discussion	The authors provide a comprehensive and fair description of the limitations. This aspect is very well summarized.	Thank you.
Peer Reviewer #2	Discussion	Page 77, Line 27: Consider replacing "affect" with "effect."	Thank you. We have edited Page 77, Line 27: from "affect" to "effect."
TEP Reviewer #4	Discussion	The major findings are clearly stated. Study limitations need to be expanded to include the aforementioned limitations. The future research section is not helpful. The use of a single definition is suggested but not a recommendation of which definition should be used or how best to select the definition to be used. The findings of the report will be very difficult to translate into new research. From a practical standpoint, currently there is not enough funding available to meet criteria for a good study in terms of adequate sample sizes or the use of derivation cohorts.	Thank you. We have edited the future research needs section and the definitions. We have expanded the discussion of our future research needs. Additionally, we have added language in the introduction, discussion, and future research areas of the report to indicate the desire of the ME/CFS community and patients to adopt the Canadian Carruthers case definition rather than the more non-specific CFS case definitions. Unfortunately funding policies and practices is beyond the scope of this report.
Peer Reviewer #4	Discussion	Discussion/ Conclusion: the findings are stated but may be poorly derived	We have added information to the discussion and conclusions sections addressing the limitations of the evidence.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 5	Discussion	I am in complete agreement with the discussion of question 1c on p. ES-11 and p. 19. It is unfortunate that the authors were not asked to address the harms for lack of diagnosis—mis-diagnosis as some other disease. The default diagnosis used by inexperienced physicians is usually mental illness. Existing instruments such as the Consensus Canadian Criteria, can distinguish ME/CFS from depression, but most general practitioners, who are most likely to see an individual complaining of malaise and fatigue, are unaware of the CCC due to the general ignorance and neglect of medical education about ME/CFS.	Thank you. The discussion, and future research areas of the report now indicate the desire of the ME/CFS community and patients to adopt the Canadian Carruthers case definition rather than the more non-specific CFS case definitions. We have expanded our discussion of the applicability of studies and need for future research to study these most severely involved patients and highlighted that these patients were not included in most studies thus results may not apply to them. We have also discussed in the future research section that monitoring of harms and reporting of harms should be more comprehensive and transparent.
Peer Reviewer # 5	Discussion	I do not think that the limitations of the CBT data were adequately addressed. The authors have chosen to include a rather notorious study termed the PACE study in the UK. CBT and GET were used as treatment modalities, and the output was measured by subjects filling out questionnaires. The improvement that was achieved by CBT was extremely modest even though the output measure was quite subjective, mainly consisting of the subjects filling out questionnaires subjectively saying how they felt and how much they were able to do. There were no objective measures of actual changes in daily activity, despite the fact that the authors had originally proposed using actometers, which could have actually given an objective measure. The only actual objective measure—asking the patients to walk for 6 minutes and then determining how many meters they walked—showed that there was very little difference between patients receiving any of the three types of treatment, and all groups performed far more poorly than healthy controls. By highlighting CBT in their abstract as something that “improves” fatigue, function, and quality of life”, the authors ignore the inherent bias in this study that they rate as “good,” apparently because of its adequate sample size and statistical analysis.	We agree that there are some limitations to the PACE trial and have expanded our discussion of this throughout the report. That said, we continue to rate this as a methodologically good-quality trial. Quality rating (internal validity) of a trial is a multi-step process and the investigators still consider it a well conducted study despite the limitations surrounding the outcome measures.
Peer Reviewer # 5	Discussion	I am not suggesting that CBT is not at all helpful to individuals with ME/CFS. It can help with coping with a chronic illness. But the research that says it has an effect on the biological, physical function of people with ME/CFS, rather than their ability to cope or mood, is flawed because of the lack of studies in which objective measures, rather than self-reporting on questionnaires, have been used.	Thank you for your comment. We have expanded our discussion of the applicability of studies and need for future research.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 5	Discussion	Furthermore, the fact that psychological studies have received far more funding is not adequately discussed. This has resulted in most of the included studies being those that attempt psychological treatments or survey psychological conditions. Paper or phone survey studies are also more prevalent in the included studies because they are, in general, less expensive to mount. These funding biases, resulting in inclusion of more such studies rather than the inadequately funded, yet more promising, biological studies are not adequately discussed.	Thank you for your comment. We have included studies based on specific criteria listed in the methods section of the report and have added information to the future research section indicating the need for further funding of studies, other than just CBT interventions.
Peer Reviewer # 5	Discussion	The virtual absence of any discussion of the biological studies makes the future research section not easily translated into new research. Why not have a discussion of the biological research that has potential with regard to possible future identification of biomarkers, diagnosis and treatment, but due to various issues with sample size and output measures, was not included?	We have edited the discussion to draw attention to areas where research is lacking and to identify where efforts should be placed in order to better guide funding, future research, and clinical practice.
Peer Reviewer # 5	Discussion	The authors may not be aware that the definition of fibromyalgia no longer requires “trigger points” and overlaps completely with some of the ME/CFS definitions. In general, people who fulfill ME/CFS criteria who have considerable pain as one of their symptoms (pain as a symptom is in most ME/CFS definitions), qualify as having fibromyalgia, a diagnosis most individuals prefer because it “sounds” like a real illness and is one that physicians are more willing to treat. The idea that ME/CFS needs to be distinguished from depression results from the lack of a definition that requires symptoms not characteristic of depression—such as post-exertional malaise or orthostatic intolerance. It is not cost-effective to demand these illness comparative groups when so little is known about the biological differences between ME/CFS and healthy individuals. Later on in the same section the authors refer to the “cardinal features of ME/CFS such as PEM, neurocognitive status, and autonomic function.” Depressed individuals lack these cardinal features.	Thank you for your comment. We have clarified and revised distinguishing factors in the report.
Peer Reviewer # 5	Discussion	It is actually not difficult for an experienced clinician to distinguish depression and ME/CFS. The problem is that a busy physician who sees someone complaining of fatigue and malaise, whose routine blood chemistry is normal, would like to send out some biological sample for testing to get a diagnosis rather than spending scarce time with the patient to investigate the constellations of symptoms.	Thank you, noted.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 5	Discussion	I completely agree with the second paragraph under Future Research. I think this is one of the best statements of the entire report. I do not mean to imply that I think that paragraph suffices. It does not cover all the future research I believe is important (see discussion of biomarkers above). The problem is that funding in the past and at present is lacking for large studies such as the authors recommend. The reason for many of the inadequate studies is due to the necessity of researchers to seek support from non-profit organizations due to insufficient attention from NIH, which has set aside targeted funds that permit larger studies and higher funding rates for diseases much less common and/or less disabling than ME/CFS.	Thank you, noted.
Peer Reviewer #3	Discussion	The limitations of this review are not adequately stated. If they had been, it would not have been submitted for review.	We have expanded our discussion of the limitations of the review and the evidence on which it is based.
Michelle Strausbaugh	Discussion	Strong reservations about: a lack of discussion about the value of receiving a diagnosis of ME/CFS and the implication that receiving the diagnosis is harmful rather than the stigma surrounding the diagnosis in the medical community; moreover there is also a failure to adequately discuss the harms associated with being misdiagnosed with ME/CFS when patients have a different recognizable and treatable disease or with being diagnosed with a psychiatric disorder	We have added discussion of the benefit of being diagnosed; however, we did not find any studies that addressed this.
Michelle Strausbaugh	Discussion	Strong reservations about: the failure to address how the paucity of funding for ME/CFS is a strong factor in why the evidence base is so small and of such poor quality; it is worth repeating Dimmock et. al's statement that "...niggardly research funding has restricted ME research to small pilot case-control studies, with a few larger studies looming over the landscape and potentially biasing this assessment of the field as a whole..."	Thank you for your comment - unfortunately funding policies and practices are beyond the scope of this report.
Michelle Strausbaugh	Discussion	Strong reservations about: the failure to call for the use of objective data such as actigraphy in place of or in addition to self-reported measures	Thank you, noted.
Solve ME/CFS Initiative and Research Advisory Council	Discussion	Discussion The authors should add a paragraph describing the strengths and limitations of comparative effectiveness systematic reviews for medically unexplained disorders like ME/CFS where comparative little to no comparative effectiveness has been conducted.	Thank you for your comment. We agree and have emphasized in the report the limitations of the review that include the fact that many of the studies were small pilot studies of limited applicability.
Mary Dimmock	Discussion	The AHRQ Evidence Review for "ME/CFS" has recommended CBT and GET, treatments that are based on the "fear avoidance" or biopsychosocial theory of CFS, a theory adopted particularly by those who use the Oxford definition and/or study the use of CBT and GET. This theory postulates that the disease is maintained by psychosocial factors, in particular maladaptive beliefs about being ill that has led to avoidance of activity and resultant deconditioning. Treatment with CBT and GET is intended to reverse illness beliefs, activity avoidance and deconditioning. This biopsychosocial theory for CFS draws on the work of psychiatrist Dr. George	Thank you for your input on bio psychosocial theory and its history in ME/CFS. Please note that at no point in the report do we indicate that the intent of CBT is to reverse the maladaptive behavior and personality factors presumed to be driving this disease. We also do not recommend any specific type of treatment, we just present what is in

Commentator & Affiliation	Section	Comment	Response
		<p>Engel, who emphasized the importance of treating the whole patient and the need to avoid mind-body dualism by considering the role of the psychological and social factors in human disease.</p> <p>But there is a vast difference between a humane understanding that heart disease might be aggravated by stress or lead to secondary depression and the idea that a contrived behavioral trait is the sole determinant that is keeping a patient sick. In the application of the biopsychosocial theory to CFS, the factors related to disease risk, causation and “maintenance” (persistence) are almost entirely devoid of biological pathology beyond acknowledging that an infection might have initially triggered the disease. Explanations for both the risk of developing the disease and for the persistence of the disease are almost exclusively grounded in psychological and behavioral problems and ignore the substantial evidence of underlying biological pathologies. In the guise of avoiding mind-body dualism, the approach has erased the body.</p> <p>This focus on psychological and behavioral factors is so strong that it has resulted in CFS being dual listed as both a neurological disease and as a mental disorder in certain medical dictionaries and terminology systems, particularly in the U.K., in spite of the World Health Organization classifying CFS only as a neurological disease and explicitly ruling that CFS is not a mental illness. Further, a number of researchers have described CFS as the prime example of somatoform disorder/somatic symptom disorder, classified as a mental disorder in the DSM-5.</p> <p>Many organic diseases like Alzheimer and cancer can be associated with psychological issues and/or reactive depression and yet, neither of those is listed in the mental health chapters of the above referenced dictionaries and terminology systems. As Dr. Richard Sykes states in a 2002 article, the existence of a psychological issue is not sufficient reason to declare a disease to be a mental disorder. Sykes goes on to state, “There must be good grounds for thinking that particular psychological factors have a causal influence” and emphasizes, “The absence of a known physical cause is not grounds for imputing psychological causation.”</p> <p>Citing the following factors, Sykes concludes that this disease has been inappropriately cast as a psychological illness:</p> <ul style="list-style-type: none"> • Psychological problems are not always present or when they are, are a consequence of the disease and not the predominant problem; • The disease often starts with a flu-like illness from which patients do not recover; and • There is substantial evidence of biological neurological and immunological abnormalities. <p>To Sykes point, no studies have demonstrated that psychological and behavioral issues are the driving factors behind the risk of getting this disease or its ongoing</p>	<p>the literature. We do not theorize why one treatment might be beneficial or not but rather report on the existing research study outcomes, limitations, and applicability to the evidence. We have emphasized the limitations of this body of research particularly as it surrounds patient subgroups.</p>

Commentator & Affiliation	Section	Comment	Response
		<p>persistence. That is, unless one views as proof the results of studies done with Oxford, Fukuda and Reeves in which overly broad definitions and patient selection methods have selected patients with psychiatric disorders. But to do so is circular reasoning in which the presence of patients with psychiatric disorder can be expected to result in findings of significant psychiatric factors. Further, such findings are not proof that the disease described by the Canadian Consensus Criteria and ME International Consensus Criteria is driven by such psychological factors or will respond to psychological treatments.</p> <p>This Evidence Review is recommending CBT, a treatment whose therapeutic intent is to reverse the maladaptive behavior and personality factors presumed to be driving this disease. Given the points made by Sykes and the fact that predominant psychological and behavioral factors have not been proven in patients that meet the Canadian Consensus Criteria or the ME International Consensus Criteria, it is unethical and scientifically invalid to recommend such treatments for CCC and ME-ICC patients.</p>	
Mary Dimmock	Discussion	<p>This Evidence Review needs to reassess these treatment recommendations in light of the psychologicalization that has been driven by the biopsychosocial theory of CFS. Further, this Evidence Review needs to decide whether the disease being evaluated is predominantly an organic disease, albeit with reactive depression or similar psychological issues or whether it is predominantly a disease of maladaptive personality and behaviors. It is nonsensical to postulate a single clinical entity that is both at the same time.</p>	<p>Determining the underlying etiology of ME/CFS was beyond the scope of this report.</p>
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Discussion	<p>I would like to point out the enormous disparity between the number of clinical trials assessing CBT and GET, and any other treatment approach. There is an immense need for more biomedical ME/CFS research, and I do hope to see this reflected in your coming recommendations. Also, larger, definitive studies on diagnostic biomarkers are required.</p>	<p>We agree and we have indicated this in the discussion, applicability, and future research needs sections of the report.</p>

Commentator & Affiliation	Section	Comment	Response
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Discussion	The Review stated that the lack of a gold standard for diagnostic comparison creates “an inherent risk of bias by the opinion of experts,” such as the identification of PEM as a critical feature without methods for testing and monitoring the symptom. However, this is a very one-sided view of bias. For example, a small number of researchers hold to the “fear avoidance theory” and/or “deconditioning and exercise intolerance theories of chronic fatigue syndrome” despite evidence to the contrary in patients with ME. On the other hand, there is a growing body of evidence around PEM and how to measure its effects, as well as objective proof of the phenomenon. Competing schools of thought are to be expected in areas of scientific controversy, but bias in the face of contradictory evidence is something different. The Evidence Review should acknowledge the risk of bias among all experts, and also explicitly acknowledge the objective evidence that contradicts such bias.	Thank you for your comment. We have expanded our discussion of the limitations of the evidence and our review, including potential biases.
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Discussion	The Review failed to acknowledge that the most severely affected patients are unlikely to participate in studies like the ones included in this Review. To assume the widest possible definition means you draw conclusions about a population whose characteristics are unclear and even in part contradictory in diagnosis. Even with a more narrow definition, many studies lack data on severe cases of ME/CFS. With using the maximum population, that imbalance is getting even worse. This is an immense problem that has to be addressed adequately before the Review is issued in its final form. Most importantly, these patients are at an exponentially higher risk for great and irreversible harm when subjected to inappropriate treatments.	Thank you for your comment. We have addressed the limitations of the current body of research and the need for more research in our future research section.

Commentator & Affiliation	Section	Comment	Response
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	Discussion	I would like to point out the enormous disparity between the number of clinical trials assessing CBT and GET, and any other treatment approach. There is an immense need for more biomedical ME/CFS research, and I do hope to see this reflected in your coming recommendations. Also, larger, definitive studies on diagnostic biomarkers are required. Also, I'm concerned by the lack of mention/discussion of possible subgroups based on differences in biological pathologies. This is a critical issue, especially when accepting eight disparate ME or CFS definitions as equivalent. ME/CFS is a complex disease, and it demands expertise. It cannot be successfully evaluated by a panel of non-experts, based on a seriously flawed Review.	Thank you for your comment. We agree that there is need for more research. The purpose of our review is to add to content of available data for providers, not to substitute for clinical judgment.
Public Reviewer # 52	Discussion	ME/CFS patients have been ignored for decades. Now when we have a glimmer of hope this review is about to put the nail in the coffin of any potential for meaningful treatment. The inclusion of the Oxford definition and approval of the PACE trial will cause more harm than good.	Thank you for your comments. We have expanded our discussion of the limitations of the PACE trial and the studies on CBT in general. We have also addressed the limits of the studies that used the Oxford criteria for enrollment.
Public Reviewer # 42	Discussion	Page ES25 I dont understand what more involved means in this sentence a smaller but more involved subset of the broader population Page ES29 States that studies using the Oxford criteria have been included in this report but that the Oxford Criteria may not be a suitable criteria to use. If this is the case the studies using this unsuitable criteria should be clearly marked and their influence on this studies conclusion made clear. Alternatively studies using unsuitable criteria could be left out of this review	Thank you for your comment. We have highlighted the differences in case definitions in Key Question 1 and edited the Key Question 2 sections to highlight the case definitions used in the particular studies. We have also expanded our discussion of the associated limitations.
Public Reviewer # 41	Discussion	I suggest reading about what has already been done at the link provided in the references section below.	Thank you.

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Public Reviewer # 43	Discussion	I kid you NOT the suffering of this illness is IMMENSE. It is like a cross between AIDS and MS. I have primary immune deficiency that causes reactivation of viruses and has travelled to my Central Nervous System in my BRAIN causing inflammation and swelling hence the name Myalgic Encephamyelitis which means All over muscle and brain swelling. My pain is so severe it feels like the muscles are ripping away from the bone. It is unending and I do NOT take pain medicine for it I take tylenol. My cytokines are sky high and that means my glands in my neck are so swollen that at times it is hard to turn my head. I have trouble walking sleeping and I cannot work. I certainly cannot fight infection My head severely hurts me its like constant migraine. I have night seizures because my brain has to release all of the pressure. I frequently fall because my legs get wobbly. I have trouble standing because I will faint. The blood flow of my whole body is affected because the swelling in my veins and arteries are affected. Which is why my vagus nerve in the autonomic nervous system causes me to faint when I get up to the bathroom in the night.	Thank you for sharing your story.
Denise Ready	Discussion	This Review brings into sharp relief the widespread confusion on the nature of ME and the inappropriateness of having nonexperts attempt to unravel a controversial and conflicting evidence base about which they know nothing. This Review is flawed and unacceptable. The lack of NIH funding has resulted in only 28 diagnostic studies and 9 medication studies to consider from the last 26 years. The result is widespread mishandling of disparate cohorts of patients and a proliferation of disparate and sometimes overly broad definitions all branded with the same CFS label. The studies that were funded and completed were those that studied behavioral and psychological pathology for a disease long proven to be the result of organic pathology. That the Evidence Review failed to recognize and acknowledge that case definition is crucial to future research. These are not all the same disease entity and failure to recognize that fact at this juncture will result in the next 26 years of research being an inconclusive waste of money and time for those one million impacted by these ill defined diseases with no treatment and no cure.	Thank you for your comment. One of the goals of the review is to identify the research gaps and we have expanded our discussion of this. We have also highlighted the case definitions used in the various studies and expanded our discussion of the limitations of using some of the less specific definitions.
Public Reviewer #5	Discussion	This study shows that there are quite many definitions of MECFS some of which are mutually contradictory and that the scope of definitions varies. It also shows there is a lack of research. That is not news to anyone interested in the matter. It is well nigh impossible to read and analyze all research on a subject. To select 914 out of 5902 potentially relevant articles Section Structured Abstract paragraph Results page v seems reasonable unless you have hundreds of qualified researchers. However that also means that the choice of criteria used for selecting the sources for this study is extremely important. Selecting studies becomes rather risky when there are so many different definitions of what MECFS is. 914 studies is a big sample. However that they would reasonably represent some typical types of research and theories in the MECFS field to me	Thank you for your comments. We have expanded our results section to highlight the case definitions used in the included studies and the limitations associated with these definitions. Of note, if we had elected to use a more specific case definition for inclusion criteria for this report, the body of evidence would have been much smaller as there is very little available. By keeping the net wide, we are hoping to shed light on not only the

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		<p>seems not certain. In the same paragraph of the Structured Abstract it is stated "Multiple case definitions have been used to define MECFS and those that require the symptoms of postexertional malaise and neurological and autonomic manifestations appear to represent a more severe subset of the broader MECFS population. To speak of the broader MECFS population is pointless. If you have say 8 different definitions you have 8 overlapping but different populations. What is that broader population? Is it denoted by the widest of the definitions or is it a new definition encompassing all the old ones? Does it include everybody that claim they suffer from MECFS plus those that against their will are diagnosed with it? That may be the object of the 914 or 5902 studies surveyed in this study but that does not give anyone much clue what MECFS is or how it is manifested. In the context of this broad study there is only one use of the broader MECFS population that would make sense. That is if you accept the broadest possible definition of MECFS. It does appear to me that this study does that. Assuming things under the heading Results. That is not good practice. If this study was an theoretical overview or analysis of theories and how they relate to each other it would be fine. But since it looks at e.g. eventual benefits of certain treatments the definition of the assumed MECFS population is crucial. Speaking of the broadest population means you talk about a multitude of populations. In my opinion it would be best to focus on the existing narrowest definition. It might be too narrow or too wide but that seems to be a reasonable starting point. To assume the widest possible definition means you draw conclusions about a population whose characteristics are unclear and even in part contradictory in diagnosis. Even with a more narrow definition many studies lack data on severe cases of MECFS. With using the maximum population that lack of data makes the imbalance even worse. Here I would add that the postexertional malaise that is mentioned in the quote above is the key characteristic of MECFS. If that is not a criteria the all sorts of fatigues are included and the object of study is illdefined. In the aforementioned Structured Abstract Section Results only three treatments are mentioned and they seem to be the only ones to have any measurable documented effect according to this study. There is no mention in Results of what subsection of the broader MECFS population these treatments have had an effect on which is a glaring omission since the definition is wide and/or unclear. To be noted there is also mention of adverse effects of CBT/GET in the same paragraph. It does read like some blindfolded individual throwing a bunch of arrows without beforehand clearly defining the target and then declare success for some arrows. I would like to thank AHRQ for putting resources into this study. It does show that there is an urgent need for research on MECFS. Such research might also shed light on more general questions such as autoimmunity. There are many who suffer greatly without getting much help. To claim a general success of behavioural therapies or any therapy in the current state of research for this</p>	<p>treatment benefits, but also the limitations and needs for future research to help move this field of study forward.</p>

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		broader population is misleading. Its like making an general overview of cancer and then concluding that mastectomy works. Again the Result paragraph does mention adverse effects of CBTGET but successfailure is not given any contextualization. There are a few other therapies that help some individuals but not all and they are not mentioned as having any value.	
TEP Reviewer #6	Conclusion	The implications are clear. We need better ME/CFS research. The report does quite a good job of identifying major limitations of the studies reviewed. However, perhaps a stronger statement concerning the implications of inadequate and/or improperly applied diagnostic criteria for treatment trials is warranted.	Thank you for your comment. We have expanded on the limitations of the evidence in the discussion.
TEP Reviewer #6	Conclusion	The report does quite rightly raise the issue of exclusion criteria being appropriately described and applied. However the significance of this is not adequately addressed, e.g., in the PACE trial the rationale for GET is that patients are deconditioned. The implication is that ME/CFS =deconditioning. This is a contentious issue in the ME/CFS community (see also CBT and psychosomatic symptoms). If deconditioning as an explanation for fatigue-related symptoms is not ruled out then deconditioned rather than ME/CFS subjects may be enrolled in the study and respond positively to GET. The problem then arises when GET becomes generally prescribed for treatment of ME/CFS when is only really applicable to the treatment of deconditioning. Validity of 6 min walk test for purposes used in the study is also questionable.	Thank you for your comment. We agree that there are some limitations to studies such as the PACE trial and have expanded our discussion of this throughout the report.
TEP Reviewer #6	Conclusion	Future research section is not really helpful. I believe this is the province of persons with expertise in ME/CFS and/or similar conditions. Two keys will accurate diagnosis and/or subgrouping (i.e., objective biomarkers)	Noted. We have revised the future research section.
Public Reviewer # 7	Conclusion	The Draft Report states that "the negative effects of being given a diagnosis of ME/CFS appear to be more universal". It is not clear what these supposed negative effects are, and should be made more clear in the summary.	We have clarified this in the discussion.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 50	Conclusions	<p>Problems with Draft Conclusions</p> <p>The Draft Report specifically acknowledges problems with both the Oxford definition and the CBT and GET results. However, the two Conclusions sections inexplicably go on to highlight CBT and GET as the most [ES-80] or even the only [vi] potentially beneficial ME/CFS treatment. That is no small mistake. If this Draft Report truly lives up to its stated goal of informing health providers and insurers on the state of ME/CFS research, it will provide the entire medical community with a fundamentally inaccurate view of the field. With all the most promising research developments wiped out by the Draft Report's exclusion criteria, gone are all the studies on potential biomarkers and quantifiable physical changes. The potential promise of immune modulators and of drugs like antivirals and antibiotics receives some discussion in the Executive Summary text [see, e.g., ES-27], but potential pharmaceutical treatments receive no mention at all in the final Conclusions [pages v, 80]. Anyone using this Draft Report, as expected, to develop clinical practice guidelines or as a basis to determine reimbursement or coverage policies [see ii] will rely on the Conclusions to take away a message that only CBT and possibly GET could successfully treat ME/CFS. And so most doctors will be more than happy to continue ignoring a disease that many falsely believe is all in patients' heads, and insurers will be thrilled to have a reason to deny claims for expensive, potentially beneficial medications in favor of much cheaper therapy-based solutions. Meanwhile, a million people – most of them unable to work and many unable to even leave their homes or their beds because of this devastating illness – will continue to wait in vain for treatment.</p> <p>It is because of these misleading and potentially dangerous conclusions that the patient community strongly objects to the current Draft Report. The final report must reverse its current reliance on flawed and discredited studies like the PACE trials and any other study based on the Oxford definition. Ideally, the final report also will do a better job of at least acknowledging the many promising areas of research not currently discussed in the report. At a bare minimum, the Conclusion sections must be rewritten to better reflect the serious concerns regarding CBT and GET studies as acknowledged elsewhere in the Draft Report itself.</p>	<p>Thank you for your comments.</p> <p>The scope of this report was not to review etiology but rather to help inform on aspects of diagnosis and treatment of the syndrome ME/CFS. When biomarker studies reported on diagnostic accuracy or ways of correctly identifying patients with ME/CFS and those without, these studies were reported. We recognize that the biomarker studies may eventually provide insight into the etiology and potentially diagnosis of ME/CFS but its work is still in its infancy for diagnosing the syndrome of ME/CFS and has not been well studied in a way that reports diagnostic validity in patients with diagnostic uncertainty and thus did not meet our inclusion criteria.</p> <p>The purpose of this review is to determine which treatments show benefit or harm rather than to determine the mechanism of how their effect occurs. We recognize that there are several theories pertaining to the mechanisms of action of these interventions; however, this is beyond the scope of the review. The comment regarding the basis for reimbursement and coverage policies is a disclaimer by AHRQ rather than an endorsement that the report should be used as such.</p>
Peer Reviewer #1	References	Ref. Leading article. A new clinical entity? Lancet 1956; 1:789-790.	Thank you for this historical perspective.
Peer Reviewer #1	References	. Henderson DA, Shelokov A. Epidemic neuromyasthenia; clinical syndrome. N Engl J Med. 1959 Apr 9;260(15):757-64.	Thank you for this historical perspective.
David Egan	References	The lancet, Volume 266, Issue 6886, Pages 394- 395, 20 August 1955.	Thank you for this historical perspective.
David Egan	References	Dr. Ramsey http://www.cfids-me.org/ramsay86.html	Thank you for this historical perspective.
David Egan	References	Dr. Acheson http://www.me-ireland.com/Acheson1959.pdf	Thank you for this historical perspective.

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David Egan	References	Dr. Richardson http://www.cfstreatmentguide.com/blog/category/whos%20who%20in%20the%20cfsme%20communitya97fd2fd3b	Thank you for this historical perspective.
Peter White Queen Mary University of London, UK	References	Brimmer, D. J., Maloney, E., Devlin, R., Jones, J. F., Boneva, R., Nagler, C. & Unger, E. R. (2013). A pilot registry of unexplained fatiguing illnesses and chronic fatigue syndrome. BMC research notes,2013; 6(1): 1-11.	Included study.
Peter White Queen Mary University of London, UK	References	Devasahayam A, Lawn T, Murphy M, White PD. Alternative diagnoses to chronic fatigue syndrome in referrals to a specialist service: a service evaluation survey. Journal of the Royal Society of Medicine Short Reports 2012;3:4. DOI 10.1258/shorts.2011.011127	Included study.
Peter White Queen Mary University of London, UK	References	Hamilton WT, Gallagher AM, Thomas JM, White PD. The prognosis of different fatigue diagnostic labels: a longitudinal survey. Family Practice 2005;22:383-388.	Background only, no data for evidence.
Peter White Queen Mary University of London, UK	References	Huibers MJ, Wessely S. The act of diagnosis: the pros and cons of labelling chronic fatigue syndrome. Psychol Med 2006;36:895-900	Background only, no data for evidence.
Peter White Queen Mary University of London, UK	References	Lawn T, Kumar P, Knight B, Sharpe MC, White PD. Psychiatric misdiagnoses in patients with chronic fatigue syndrome. Journal of the Royal Society of Medicine Short Reports. 2010;1:28. DOI 10.1258/shorts.2010.010042. http://shortreports.rsmjournals.com/content/1/4/28.full	Included study.
Peter White Queen Mary University of London, UK	References	Newton JL, Mabillard H, Scott A, Hoad A, Spickett G. The Newcastle NHS Chronic Fatigue Service: not all fatigue is the same. J R Coll Physicians Edin 2010;40:304-7	Included study.
Peer Reviewer #2	References	Black CD, O' Connor PJ, McCully KK. Increased daily physical activity and fatigue symptoms in chronic fatigue syndrome. Dyn Med. 2005 Mar 3;4(1):3. PMID: 15745455	Inadequate duration (<12 weeks)
Peer Reviewer #2	References	Black CD, McCully KK. Time course of exercise induced alterations in daily activity in chronic fatigue syndrome. Dyn Med. 2005 Oct 28;4:10.	Inadequate duration (<12 weeks)
Peer Reviewer #2	References	Davenport TE, Stevens SR, VanNess MJ, Snell CR, Little T. Conceptual model for physical therapist management of chronic fatigue syndrome/myalgic encephalomyelitis. Phys Ther. 2010;90(4):602-614. PMID: 20185614.	Background only, no data for evidence.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	References	International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME). Chronic fatigue syndrome/myalgic encephalomyelitis. A primer for clinical practitioners. Chicago (IL): International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME); 2012. 41 p. [121. references]http://mc.manuscriptcentral.com/ehc?URL_MASK=0f3534e90eee41c99adebe3242213fbc.	Reviewed for background.
Public Reviewer # 39; Sten Helmfrid; Parekh	References	Carruthers BM, Jain AK et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. J Chronic Fatigue Syndr. 2003;11(1): 7-115.	Background paper only, no data for evidence.
Public Reviewer # 39,; Agardy; Marj van de Sande; Sister Sandra Duma, OSF, MS Ed; Parekh	References	Carruthers BM, van de Sande MI et al. Myalgic encephalomyelitis: International Consensus Criteria. J Intern Med 2011; 270:327–38. http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02428.x/full	Background paper only, no data for evidence.
Public Reviewer # 39,;Marj van de Sande; Sister Sandra Duma, OSF, MS Ed	References	Carruthers BM, van de Sande MI et al. Myalgic Encephalomyelitis – Adult & Paediatric: International Consensus Primer for Medical Practitioners. Published online October 2012. http://www.name-us.org/DefintionsPages/DefinitionsArticles/2012_ICC%20primer.pdf	Used to inform background.
Public Reviewer # 39	References	Gilliam, A. G. Epidemiological Study on an Epidemic, Diagnosed as Poliomyelitis, Occurring Among the Personnel of Los Angeles County General Hospital During the Summer of 1934. United States Treasury Department Public Health Service Public Health Bulletin, US Treasury Dept. No. 240. Washington, DC: United States Government Printing Office.1938.	Out of date range for included papers.
Public Reviewer # 39; Dimmock et al.	References	Jason LA, Brown A, Evans M, et al. Contrasting chronic fatigue syndrome versus myalgic encephalomyelitis/chronic fatigue syndrome. Fatigue. 2013;1(3)PMID: 23914329.	Paper included as evidence.
White, Chalder, Moss-morris, Sharpe & Wearden; White	References	Brimmer, D. J., Maloney, E., Devlin, R., Jones, J. F., Boneva, R., Nagler, C. & Unger, E. R. (2013). A pilot registry of unexplained fatiguing illnesses and chronic fatigue syndrome. BMC research notes,2013; 6(1): 1-11.	Wrong type of study for included evidence.
White, Chalder, Moss-Morris, Sharpe & Wearden	References	Dougall D, Johnson AL, Goldsmith K, Sharpe M, Angus B, Chalder T, White PD. Adverse events and deterioration reported by participants in the PACE trial of therapies for chronic fatigue syndrome. Journal of Psychosomatic Research 2014; 77: 20-26.	Paper included as evidence.

Commentator & Affiliation	Section	Comment	Response
White, Chalder, Moss-morris, Sharpe & Wearden	References	Fulcher KY, White PD. Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. <i>BMJ</i> 1997; 314: 1647–52.	Paper included as evidence.
White, Chalder, Moss-morris, Sharpe & Wearden	References	Gladwell PW, Pheby D, Rodriguez T, Poland F. Use of an online survey to explore positive and negative outcomes of rehabilitation for people with CFS/ME. <i>Disability and Rehabilitation</i> 2014; 36: 387-394.	Wrong study design.
White, Chalder, Moss-morris, Sharpe & Wearden; Agardy	References	Moss-Morris R, Sharon C, Tobin R, Baldi JC. A randomized controlled graded exercise trial for chronic fatigue syndrome: outcomes and mechanisms of change. <i>J Health Psychol</i> 2005; 10: 245–59.	Paper included as evidence.
White, Chalder, Moss-morris, Sharpe & Wearden	References	Powell, P., Bentall, R. P., Nye, F. J., & Edwards, R. H. T. (2001). Randomized controlled trial of patient education to encourage exercise in chronic fatigue syndrome. <i>BMJ</i> 2001; 322, 1–5.	Wrong population (children and adolescents, patients with other underlying diagnosis, not applicable to clinical setting).
White, Chalder, Moss-morris, Sharpe & Wearden	References	Wallman, K. E., Morton, A. R., Goodman, C., Grove, R., & Guilfoyle, A. M. Randomised controlled trial of graded exercise in chronic fatigue syndrome. <i>The Medical Journal of Australia</i> , 004; 180, 444–448.2	Wrong population (children and adolescents, patients with other underlying diagnosis, not applicable to clinical setting).
White, Chalder, Moss-morris, Sharpe & Wearden; Dimmock et al.	References	Wearden AJ, Morriss RK, Mullis R et al. Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. <i>Br J Psychiatry</i> 1998; 172: 485–90.	Paper included as evidence.
White, Chalder, Moss-morris, Sharpe & Wearden; Agardy; Tom Kindolon; Charmian Proskauer; Dimmock et al	References	White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, Baber HL, Burgess M, Clark LV, Cox DL, Bavinton J, Angus BJ, Murphy G, Murphy M, O'Dowd H, Wilks D, McCrone P, Chalder T, Sharpe M, and on behalf of the PACE trial management group. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. <i>The Lancet</i> 2011;377:823-36.	Paper included as evidence.
White; Dimmock et al.	References	Devasahayam A, Lawn T, Murphy M, White PD. Alternative diagnoses to chronic fatigue syndrome in referrals to a specialist service: a service evaluation survey. <i>Journal of the Royal Society of Medicine Short Reports</i> 2012;3:4. DOI 10.1258/shorts.2011.011127	Paper included as evidence.
White	References	Hamilton WT, Gallagher AM, Thomas JM, White PD. The prognosis of different fatigue diagnostic labels: a longitudinal survey. <i>Family Practice</i> 2005;22:383-388.	Out of scope of review.

Commentator & Affiliation	Section	Comment	Response
White	References	Huibers MJ, Wessely S. The act of diagnosis: the pros and cons of labelling chronic fatigue syndrome. <i>Psychol Med</i> 2006;36:895–900	Background paper only, no data for evidence.
White; Charmian Proskauer; Dimmock et al.	References	Lawn T, Kumar P, Knight B, Sharpe MC, White PD. Psychiatric misdiagnoses in patients with chronic fatigue syndrome. <i>Journal of the Royal Society of Medicine Short Reports</i> . 2010;1:28. DOI 10.1258/shorts.2010.010042. http://shortreports.rsmjournals.com/content/1/4/28.full	Paper included as evidence.
White; Dimmock et al.	References	Newton JL, Mabillard H, Scott A, Hoad A, Spickett G. The Newcastle NHS Chronic Fatigue Service: not all fatigue is the same. <i>J R Coll Physicians Edin</i> 2010;40:304–7	Paper included as evidence.
Public Reviewer # 56	References	3. Wearden AJ, Emsley R J, Mediators of the effects on fatigue of pragmatic rehabilitation for chronic fatigue syndrome, <i>Consult Clin Psychol</i> . 2013 Oct; 81(5):831-8. doi: 10.1037/a0033561. 2013 Jun 24.	Paper included as evidence.
Public Reviewer # 56; Dimmock et al.; Sten Helmfrid; Public Reviewer # 51	References	5. Snell CR, Stevens SR, Davenport TE, Van Ness JM (213) Discriminative Validity of Metabolic and Workload Measurements to Identify Individuals With Chronic Fatigue Syndrome. <i>Physical Therapy</i> 27 June 2013 10.2522/ptj.20110368 <i>Physical Therapy</i>	Background paper only, no data for evidence.
Public Reviewer # 56; Dimmock et al.; Sister Sandra Duma, OSF, MS Ed	References	6. Van Ness JM, Snell CR, Stevens SR, Diminished Cardiopulmonary Capacity During Post-Exertional Malaise. <i>Journal of Chronic Fatigue Syndrome</i> , Vol. 14(2) 2007 (c.) 2007 by The Haworth Press. All rights reserved. doi:10.1300/J092v14n02_07 77	Wrong publication type (opinions, letters to the editor, conference proceedings, abstract only).
Public Reviewer # 56; Dimmock et al.	References	7. Van Ness JM, Snell CR, Strayer DR, Dempsey L, Stevens SR, Subclassifying chronic fatigue syndrome through exercise testing. <i>Medicine & Science in Sports & Exercise</i> (impact factor: 4.43). 06/2003; 35(6):908-13. DOI:10.1249/01.MSS.0000069510.58763.E8	Discussion paper only (clinical subgroups, see above), no data for evidence.
Public Reviewer # 56; Anonymous; Dimmock et al.; Sten Helmfrid	References	8. Keller BA, Pryor JL, Giloteaux L Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO2peak indicates functional impairment <i>J Transl Med</i> . 2014; 12: 104 Published online Apr 23, 2014. doi: 10.1186/1479-5876-12-104 PMID: PMC4004422	Wrong study design.
Public Reviewer # 56; Sten Helmfrid	References	10. Sharpe MC, Archard LC, Banatvala JE et al . A report-chronic fatigue syndrome: guidelines for research. <i>J R Soc Med</i> . 1991;84(2): 118-21 PMID: 1999813.	Wrong publication type (opinions, letters to the editor, conference proceedings, abstract only).
Public Reviewer # 56; Charmian Proskauer; Dimmock et al.	References	11. White PD, Goldsmith K, Johnson AL, Chalder T, Sharpe M; Psychological Medicine, 43 (2013b). Letter to the Editor Response to correspondence concerning `Recovery from chronic fatigue syndrome after treatments in the PACE trial' . <i>Journal of Psychological Medicine</i> August 2013 Volume 43 /doi:10.1017/S0033291713001311	Wrong publication type (letter).

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 56; Charmian Proskauer; Dimmock et al.; Public Reviewer # 51	References	12. White PD, Goldsmith K, Johnson AL, Chalder T, Sharpe M; PACE Trial Management Group (2013). Recovery from chronic fatigue syndrome after treatments given in the PACE trial. Psychological Medicine Jan 31: 1-9 available on CJO2013. doi:10.1017/S0033291713000020.	Paper included as evidence.
Public Reviewer # 56; Sten Helmfrid	References	13. Lipkin DP, Scriven AJ, Crake T, Poole-Wilson PA (1986). Six minute walking test for assessing exercise capacity in chronic heart failure. British Medical Journal 292, 653-5.	Wrong population.
Public Reviewer # 56; Charmian Proskauer; Dimmock et al.; Sten Helmfrid	References	14. Kadikar A, Maurer J, Kesten S (1997). The six-minute walk test: a guide to assessment for lung transplantation. The Journal of heart and lung transplantation 16, 313-9.	Wrong intervention.
Public Reviewer # 56	References	15. Agardy S (2013). Comments on `Recovery from chronic fatigue syndrome after treatments given in the PACE trial' [letter] Psychological Medicine / Volume 43 / Issue 08 / August 2013, pp 1787-1787, Published online: 19 July 2013	Wrong publication type (letter).
Public Reviewer # 56	References	16. Maryhew C (2013) Comments on 'Recovery from chronic fatigue syndrome after treatments given in the PACE trial' [Letter] Psychological Medicine doi:10.1017/ S0033291713001293 PACE Trial: letters and reply Journal of Psychological Medicine 1789-90 August 2013	Wrong publication type (letter).
Public Reviewer # 56	References	17. Shepherd C (2013) Comments on `Recovery from chronic fatigue syndrome after treatments given in the PACE trial' [Letter]. Psychological Medicine doi:10.1017/ S003329171300113X	Wrong publication type (letter).
Public Reviewer # 56; Public Reviewer # 51	References	18. Agardy S 'Recovery' in PACE, the 6 Minute Walking Test and Other Issues How Well Can 'Recovered' Patients Walk? co-cure Archives, 12 Aug 2013 https://listserv.nodak.edu/cgi-bin/wa.exe?A2=ind1308b&L=co-cure&F=&S=&P=9449	Discussion paper only, no data for evidence.
Public Reviewer # 56; Erica Verrilio?; Public Reviewer # 51	References	19. Voices from the Shadows, http://voicesfromtheshadowsfilm.co.uk/	Excluded, not evidence. Reviewed by team members for contextual information.
Public Reviewer # 56	References	20. Sheridan A, Raw data for 6mwt, Freedom of Information request to Queen Mary, University of London. https://www.whatdotheyknow.com/request/raw_data_for_6mwt	Wrong publication type.
Peer Reviewer #2	References	Black CD, O' Connor PJ, McCully KK. Increased daily physical activity and fatigue symptoms in chronic fatigue syndrome. Dyn Med. 2005 Mar 3;4(1):3. PMID: 15745455	Inadequate duration (<12 weeks).
Peer Reviewer #2; Dimmock et al.	References	Black CD, McCully KK. Time course of exercise induced alterations in daily activity in chronic fatigue syndrome. Dyn Med. 2005 Oct 28;4:10.	Inadequate duration (<12 weeks).

Source: <http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2004>
Published Online: December 9, 2014

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	References	Davenport TE, Stevens SR, VanNess MJ, Snell CR, Little T. Conceptual model for physical therapist management of chronic fatigue syndrome/myalgic encephalomyelitis. <i>Phys Ther.</i> 2010;90(4):602-614. PMID: 20185614.	Background paper only, no data for evidence.
TEP Reviewer #4; Anonymous	References	International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME). Chronic fatigue syndrome/myalgic encephalomyelitis. A primer for clinical practitioners. Chicago (IL): International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME); 2012. 41 p. [121. references] Use: http://www.iacfsme.org/Portals/0/PDF/PrimerFinal3.pdf	Background paper only, no data for evidence.
Maureen Hansen	References	Rituximab was given to small group of patients, with remarkable effect in some. But rituximab is not given for 12 weeks—is this why it was excluded? http://www.ncbi.nlm.nih.gov/pubmed/22039471	Excluded for duration <12 weeks. Included in discussion of medications.

Commentator & Affiliation	Section	Comment	Response
Maureen Hansen	References	Activity or characteristics of immune cells http://www.ncbi.nlm.nih.gov/pubmed/23514202 , http://www.ncbi.nlm.nih.gov/pubmed/22571715 , http://www.ncbi.nlm.nih.gov/pubmed/21619669 , http://www.ncbi.nlm.nih.gov/pubmed/20520837 Gene expression profiles in serum or immune cells http://www.biomedcentral.com/1472-6793/5/5 , http://www.ncbi.nlm.nih.gov/pubmed/24054763 , http://www.ncbi.nlm.nih.gov/pubmed/22210239 , http://www.ncbi.nlm.nih.gov/pubmed/22572093 , http://www.ncbi.nlm.nih.gov/pubmed/22110941 , http://www.ncbi.nlm.nih.gov/pubmed/21615807 , http://www.ncbi.nlm.nih.gov/pubmed/19647494 Brain or heart imaging http://www.ncbi.nlm.nih.gov/pubmed/20661876 , http://www.ncbi.nlm.nih.gov/pubmed/21793948 , http://www.ncbi.nlm.nih.gov/pubmed/22281935 , Cerebrospinal fluid protein profiles http://www.ncbi.nlm.nih.gov/pubmed/16321154 , http://www.ncbi.nlm.nih.gov/pubmed/21383843 Differences in physiological or autonomic response to exercise http://www.ncbi.nlm.nih.gov/pubmed/24456560 , http://www.ncbi.nlm.nih.gov/pubmed/23813081 , http://www.ncbi.nlm.nih.gov/pubmed/20095909 Autonomic dysfunction tests, such as tilt-table http://www.ncbi.nlm.nih.gov/pubmed/23388153 , http://www.ncbi.nlm.nih.gov/pubmed/23206180 Serum or cell metabolite profiles http://www.ncbi.nlm.nih.gov/pubmed/22728138 Mitochondrial function http://www.ncbi.nlm.nih.gov/pubmed/22837795 Microbiome profiles http://www.ncbi.nlm.nih.gov/pubmed/19567398 , http://www.ncbi.nlm.nih.gov/pubmed/23791918	These articles are not for diagnosis and do not meet inclusion criteria.
Maureen Hansen	References	This is not true, as can be seen in non-reviewed studies http://www.ncbi.nlm.nih.gov/pubmed/20937116 , http://www.ncbi.nlm.nih.gov/pubmed/23813081 . Both objective CPETs, actometers, and survey forms can monitor this symptom.	Background paper only, no data for evidence.
Elizabeth Potter	References	I am in support of the response by Mary Dimmock, Claudia Goodell, Denise Lopez-Majano, Jennie Spotila and Erica Verillo that is posted on Occupy CFS; http://www.occupycfs.com/2014/10/15/evidence-review-comments-preview/	Noted.
Anonymous	References	G. Hallmann, R. Coutts, Y. Hartmann; "ME/CFS: Trauma in the Context of Social Institutions", "ME/CFS: Social Security Accessibility and Experiences", "ME/CFS: Institutional Dependence" (2014). http://www.iacfsme.org/DesktopModules/DigitalDownload/2014Syllabus25.pdf	Reviewed, not evidence.

Commentator & Affiliation	Section	Comment	Response
Anonymous	References	EJ Dansie, P Heppner, H Furberg, J Goldberg, D Buchwald, N Afari; "The Comorbidity of Self-Reported Chronic Fatigue Syndrome, Post-Traumatic Stress Disorder, and Traumatic Symptoms" (2012) http://www.nimh.nih.gov/health/topics/post-traumatic-stress-disorder-ptsd/index.shtml	Reviewed, not evidence.
Anonymous	References	"Results from the Canadian Community Health Survey (CCHS) 2005, 2010 and 2012" http://www.meao.ca/files/Academic_Clinical_Perspectives.pdf http://www.un.org/disabilities/convention/conventionfull.shtml	Reviewed, not evidence.
Anonymous	References	I urge AHRQ to address physical harms and psychological trauma experienced by individuals with ME/CFS, especially in regard to "therapy" protocols and false beliefs by medical personnel and insurers. I urge AHRQ to correct the errors identified by Jennie Spotila et al., Tom Kindlon, and Public Reviewer # 39: https://dl.dropboxusercontent.com/u/57025850/Comments%20on%20AHRQ%20Evidence%20Review%20Part%201of2%20Final.pdf https://dl.dropboxusercontent.com/u/57025850/Comments%20on%20AHRQ%20evidence%20review%20Part%202of2%20Final.pdf http://www.twitlonger.com/show/n_1sd5m0a https://drive.google.com/file/d/0B4uD-VyWmlw2bUt0LWlnMzl1Um8/view?pli=1	Comments were received during the comment period. These are links to those comments.
Anonymous	References	Balint et al. 2006; Clin Rheumatol; "A brief history of medical taxonomy and diagnosis"	Reviewed, not evidence.
Tom Kindlon, Anonymous	References	Mundt JC1, Marks IM, Shear MK, Greist JH. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. Br J Psychiatry. 2002 May;180:461-4. http://bjp.rcpsych.org/content/180/5/461.long	Validation paper for Work and Social adjustment scale. Not evidence, included as a reference for appendix J.
Tom Kindlon	References	PLoS One. 2012;7(8):e40808. doi: 10.1371/journal.pone.0040808. Epub 2012 Aug 1. Adaptive pacing, cognitive behaviour therapy, graded exercise, and specialist medical care for chronic fatigue syndrome: a cost-effectiveness analysis. McCrone P1, Sharpe M, Chalder T, Knapp M, Johnson AL, Goldsmith KA, White PD. http://www.plosone.org/article/info:doi/10.1371/journal.pone.0040808	Cost-effectiveness was out of the scope of this review.
Tom Kindlon	References	O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A. Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme. Health Technol Assess. 2006 Oct;10(37):iii-iv, ix-x, 1-121. http://www.journalslibrary.nihr.ac.uk/hta/volume-10/issue-37	This study is included.
Tom Kindlon	References	79. Deale A, Husain K, Chalder T, et al. Long-term outcome of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. Am J Psychiatry. 2001;158(12): 2038-42. PMID: 11729022.	This study is included.
Tom Kindlon	References	The CDC's 2003 population-based study Reyes M, Nisenbaum R, Hoaglin DC, Unger ER, Emmons C, Randall B, Stewart G, Abbey S, Jones JF, Gantz N, Minden S, Reeves WC. Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas. Archives of Internal Medicine 2003;163:1530-1536 found that a delayed diagnosis was a risk factor for poor prognosis.	Noted.

Commentator & Affiliation	Section	Comment	Response
Tom Kindolon	References	Woodward RV, Broom DH, Legge DG. Diagnosis in chronic illness: disabling or enabling--the case of chronic fatigue syndrome. J R Soc Med. Jun 1995; 88(6): 325–329.	Out of scope of review.
Charmian Proskauer	References	For further reports on harms from GET, please see Reporting of Harms Associated with Graded Exercise Therapy and Cognitive Behavioural Therapy in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, T. Kindlon, Bull. IACFS/ME: 19 (2), Fall 2011. This important paper was omitted from your review because it appeared in a non-indexed journal (“gray literature”). The paper should be evaluated on its merits and its evidence for harms cited in the report.	This is a non-systematic report of harms from CBT and GET. There is no original data.
Charmian Proskauer	References	would draw your attention to the following by Fred Friedberg, PhD, President, International Association for CFS/ME: http://iacfsme.org/PACETrial/tabid/450/Default.aspx	Review of PACE trial, not evidence.
Charmian Proskauer, Dimmock et al.	References	Cella M, White PD, Sharpe M, et al. Cognitions, behaviours and co-morbid psychiatric diagnoses in patients with chronic fatigue syndrome. Psychol Med. 2013 Feb;43(2): 375-80. PMID: 22571806.	Reporting of co-morbid conditions of subjects in PACE trial. No evidence.
Charmian Proskauer, Dimmock et al.	References	White PD, Sharpe MC, Chalder t, et al. Protocol for the PACE trial: a randomized controlled trial of adaptive pacing, cognitive behavior therapy, and graded exercise, as supplements to standardized specialist medical care versus standardized specialist medical care alone for patients with the chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy. BMC Neurol. 2007;7:6. PMID: 17397525.	Protocol for PACE trial. Not evidence.
Charmian Proskauer	References	Reeves WC, Wagner D, Nisenbaum R, et al. Chronic fatigue syndrome –a clinically empirical approach to its definition and study. BMC Med. 2005;3: 19. PMID: 16356178.	Background paper only, no data for evidence.
Charmian Proskauer, Dimmock et al., Anonymous	References	McCrone P, Sharpe M, Chalder T, et al. Adaptive pacing, cognitive behavior therapy, graded exercise, and specialist medical care for chronic fatigue syndrome: a cost-effectiveness analysis. PLoS One. 2012;7(8): e40808. PMID: 22870204.	Cost-effectiveness was out of the scope of this review.
Charmian Proskauer, Dimmock et al.	References	Reeves WC, Lloyd A, Vernon SD, et al. Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. BMC Health Serv Res.2003;3(1): 25. PMID: 14702202.	Background paper only, no data for evidence.
Charmian Proskauer, Dimmock et al.	References	Goudsmit, EM. Rectification to ensure balance. http://pb.rcpsych.org/content/early/2014/07/14/pb.bp.113.045005/reply#pbrcpsyc_h_el_21243 (retrieved October 9, 2014).	Wrong publication type (comments and letters).
Anonymous	References	https://dl.dropboxusercontent.com/u/89158245/Case%20Definition%20Letter%20final%2010-25-13.pdf	Noted, not evidence.
Anonymous	References	Ramsay M: Myalgic Encephalomyelitis and Postviral Fatigue States. 2nd edition. London: Gower Medical Publishing; 1988.	Included background paper.
Anonymous	References	van der Meer, J. W. M. and Lloyd, A. R. (2012), A controversial consensus – comment on article by Broderick et al. Journal of Internal Medicine, 271: 29–31. doi: 10.1111/j.1365-2796.2011.02468.x	Wrong publication type (comment).

Commentator & Affiliation	Section	Comment	Response
Anonymous	References	Broderick, G. (2012), Response to 'A controversial consensus'; By the International Consensus Panel. Journal of Internal Medicine, 271: 213–217. doi: 10.1111/j.1365-2796.2011.02499.x	Wrong publication type (letter).
Anonymous	References	Scadding JG. Diagnosis: the clinician and the computer (Ref. 117 (p. 90) Lancet. 1967;2((7521):877-82 PMID:4168324) is used as a reference for the term 'syndrome': "a combination of symptoms and signs which have been observed to occur together so frequently and to be so distinctive that they constitute a recognizable clinical picture." The Scadding reference also discusses the natural evolution from the use of pattern recognition to one that is more rules-based [And, more amenable to the strict evidence-based medicine approach.]	Background paper only, no data for evidence.
Anonymous	References	Jason LA, Helgerson J, Torres-Harding SR, Carrico AW, Taylor RR: Variability in diagnostic criteria for chronic fatigue syndrome may result in substantial differences in patterns of symptoms and disability. Eval Health Prof 2003, 26: 3-22. (ME and CFS)	Wrong outcomes.
Anonymous	References	Jason LA, Torres-Harding SR, Jurgens A, Helgerson J. Comparing the Fukuda et al. Criteria and the Canadian case definition for chronic fatigue syndrome. J. Chronic Fatigue Syndr. 2004; 12: 37–52.	Included paper.
Anonymous	References	King C, Jason LA (2004). Improving the diagnostic criteria and procedures for chronic fatigue syndrome Biological Psychology 68 (2005) 87–106 (Looks at CDC definitions)	Background information only.
Anonymous	References	Leonard A. Jason, Meredyth Evans, Molly Brown, Nicole Porter, Abigail Brown, Jessica Hunnell, Valerie Anderson, Athena Lerch (2011). Fatigue Scales and Chronic Fatigue Syndrome: Issues of Sensitivity and Specificity Disability Studies Quarterly (2011) Vol 31 No 1	Reviewed, not evidence.
Anonymous	References	Twisk FN (2014). Myalgic Encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS): The essence of objective assessment, accurate diagnosis, and acknowledging biological and clinical subgroups. Frontiers in Physiology. accessed on October 15 2014 at http://journal.frontiersin.org/Journal/10.3389/fphys.2014.00109/full	Wrong outcome, not evidence.
Dimmock et al.	References	REFERENCES Dr. Susan Maier's presentation to the IOM Panel for Diagnostic Criteria on January 27-28, 2014 http://www.iom.edu/~media/Files/Activity%20Files/Disease/ME/CFS/Maier%20IOM%20ME/CFS%20Presentation.pdf a. How do ME and CFS differ? i. Do these illnesses lie along the same continuum of severity or are they entirely separate with common symptoms? ii. What makes them different, what makes them the same? iii. What is lacking in each case definition – do the non- overlapping elements of each case definition identify a subset of the illness or do they encompass the entirety of the population?	The Key Questions and scope were based on what can be accomplished by a systematic review process. Other speakers and experts will address the other areas of the P2P conference that cannot be covered by the evidence review.

Commentator & Affiliation	Section	Comment	Response
		<p>According to a discussion at the June 2014 CFSAC, these questions were apparently removed from the P2P evidence review protocol because there is “not enough evidence” in the literature to consider this question. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac-minutes-june-17-2014.pdf page 38</p> <p>Jason has a substantial body of evidence on this issue. Two of the articles include</p> <ul style="list-style-type: none"> – Jason, L., Richman, J., Friedberg, F., Wagner, L., Taylor, R., Jordan, K. Politics science and the emergence of a new disease. September 1997, American Psychologist. Vol. 52, No. 9, 973-983 (Exclusion code: not given) – Jason, L., Richman, J. How Science Can Stigmatize: The Case of Chronic Fatigue Syndrome Journal of Chronic Fatigue Syndrome, Vol. 14(4),2007 (Exclusion code: not given) – Jason, L., Najjar, N., Porter, N., Reh, C. Evaluating the Centers for Disease Control’s Empirical Chronic Fatigue Syndrome Case Definition. Journal of Disability Policy Studies Oct 2008, – Jason LA, Evans M, Brown A, et al. Sensitivity and specificity of the CDC empirical chronic fatigue syndrome case definition. Psychology. 2010;1(1): 9-16. PMID: 23685416. <p>Publications for the Wichita Surveillance study include</p> <ul style="list-style-type: none"> – Reyes M, Nisenbaum R, Hoaglin DC, Unger ER, Emmons C, Randall B, Stewart JA, Abbey S, Jones JF, Gantz N, Minden S, Reeves WC: Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas. Arch Intern Med. 2003 Jul 14;163(13):1530-6. (Exclusion code: not given) – Solomon L, Nisenbaum R, Reyes M, Papanicolaou DA, Unger ER, Reeves WC: Functional status of persons with chronic fatigue syndrome in the Wichita population. BMC Hlth Quality Life Outcomes 2003, 1:48. (Exclusion code: not given) – Nisenbaum R, Jones JF, Unger ER, Reyes M, Reeves WC: A population based study of the clinical course of chronic fatigue syndrome. BMC Hlth Quality Life Outcomes 2003, 1:49. (Exclusion code: 2) “ About one-third of CFS subjects retained the classification after 1 year of follow-up (Table 6). At 2 and 3 years follow-up, only 21% of the subjects were classified as having CFS. Most transitioned into a non-CFS state because of insufficient symptoms or fatigue severity, absence of fatigue, or identification of an exclusionary condition. Overall, 23.1% (15 of 65) were eventually diagnosed with permanent exclusions.” – Nisenbaum, R., Jones, J., Unger, R., Reyes, M., Reeves, W. A population-based study of the clinical course of chronic fatigue syndrome. Health Qual Life Outcomes. 2003; 1: 49. Published online Oct 3, 2003. doi: 10.1186/1477-7525-1-49 (Exclusion code: 2) – Reeves, W., Wagner, D., Nisenbaum, R., Jones, J., Gurbaxani, B., Solomon, L., 	

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Commentator & Affiliation	Section	Comment	Response
		<p>Papanicolaou, D., Unger, E., Vernon, S., Heim, C. Chronic Fatigue Syndrome – A clinically empirical approach to its definition and study. BMC Medicine 2005, 3:19 (Exclusion code: 8)</p> <p>Cairns R1, Hotoptf M. A systematic review describing the prognosis of chronic fatigue syndrome. Occup Med (Lond). 2005 Jan;55(1):20-31. (Exclusion code:2)</p> <p>Reeves et al. "Chronic Fatigue Syndrome – A Clinically Empirical Approach to Its Definition and Study" in BMC Medicine. 2005, December 15. "most studies of CFS merely note that they used the 1994 case definition and they do not generally specify how disability, fatigue and symptom occurrence were elucidated. Thus, it is difficult to assess the validity of their diagnostic criteria and essentially impossible to compare results between studies critically."</p> <p>CPET studies Include in the Review</p> <ul style="list-style-type: none"> – Davenport TE, Stevens SR, Baroni K, et al. Reliability and validity of Short Form 36 Version 2 to measure health perceptions in a sub-group of individuals with fatigue. Disabil Rehabil. 2011;33(25-26): 2596-604. PMID: 21682669. – Davenport TE, Stevens SR, Baroni K, Van Ness M, Snell CR. "Diagnostic accuracy of symptoms characterizing chronic fatigue syndrome." Disabil Rehabil. 2011 Jan 6. <p>Excluded in the Review</p> <ul style="list-style-type: none"> – VanNess JM, Stevens SR, Bateman L, Stiles TL, Snell CR. "Post-exertional malaise in women with chronic fatigue syndrome." J Womens Health (Larchmt). 2010 Feb;19(2):239-44. (Exclusion code: none provided) – Keller, B. Micale, F. Exercise Testing to Quantify Effects of Fatigue on Functional Capacity in Patients With CFS. in IACFS/ME Biennial Conference; Translating Evidence Into Practice. 2011. Ottawa, Ontario, Canada. – Vermeulen, R. Kurk, Visser, F. Sluiter, W. Scholte, H. Patients with chronic fatigue syndrome performed worse than controls in a controlled repeated exercise study despite a normal oxidative phosphorylation capacity. J Transl Med, 2010. 8: p. 93. (Exclusion code: none provided) – Cooper DM, Radom-Aizik S, Schwindt C, et al. Dangerous exercise: lessons learned from dysregulated inflammatory responses to physical activity. J Appl Physiol (1985). 2007;103(2):700-9. PMID: 17495117. (Exclusion code: 9) <p>He, J., Hollingsworth, K., Newton, J., Blamirea, A. Cerebral vascular control is associated with skeletal muscle pH in chronic fatigue syndrome patients both at rest and during dynamic stimulation Neuroimage Clin. 2013; 2: 168–173. Published online Jan 5, 2013. doi: 10.1016/j.nicl.2012.12.006. (Exclusion code: not given)</p> <p>Also see</p> <ul style="list-style-type: none"> – Hollingsworth KG, Jones DE, Taylor R, Blamire AM, Newton JL. Impaired cardiovascular response to standing in chronic fatigue syndrome. Eur J Clin 	

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		<p>Invest. 2010 Jul;40(7):608-15. doi: 10.1111/j.1365-2362.2010.02310.x. Epub 2010 May 23. (Exclusion code: 7)</p> <p>– Newton, J. "Understanding Muscle Dysfunction in M.E./CFS." Action on ME Presentation at the annual meeting, November 2013. Reported a number of findings including a large increase in acid in skeletal muscle with exercise along with a reduction in anaerobic exercise. (Exclusion code: not given)</p> <p>Light AR, White AT, Hughen RW, Light KC. Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects. J Pain. 2009 Oct;10(10):1099-112. (Exclusion code: not given)</p> <p>These studies were excluded for a variety of issues but would have added significantly to the analysis of concordance and definitional accuracy.</p> <p>– Jason LA, King CP, Richman JA, et al. U. S. case definition of chronic fatigue syndrome: Diagnostic and theoretical issues. J Chronic Fatigue Syndr. 1999;5(3-4):3-33. (Exclusion code: 2)</p> <p>– Jason LA, Sunnquist M, Brown A, et al. Examining case definition criteria for chronic fatigue syndrome and myalgic encephalomyelitis. Fatigue. 2014;2(1) (Exclusion code: 7)</p> <p>– De Becker P, McGregor N, De Meirleir K. A definition-based analysis of symptoms in a large cohort of patients with chronic fatigue syndrome. J Intern Med. 2001;250(3):234-40. PMID: 11555128 (Exclusion code: 3)</p> <p>– Jason LA, Taylor RR. Applying cluster analysis to define a typology of chronic fatigue syndrome in a medically-evaluated, random community sample. Psychol Health. 2002;17(3):323-37. (Exclusion: 3)</p> <p>– Brimacombe M, Helmer D, Natelson BH. Clinical differences exist between patients fulfilling the 1988 and 1994 case definitions of chronic fatigue syndrome. J Clin Psychol Med Settings. 2002;9(4):309-14. (Exclusion code: 8)</p> <p>– Hawk C, Jason LA, Torres-Harding S. Differential diagnosis of chronic fatigue syndrome and major depressive disorder. Int J Behav Med. 2006;13(3):244-51. PMID: 17078775. (Exclusion code: 8)</p> <p>– Jason, L., Sunnquist, M., Brown, A., Evans, M., Newton, J. Are Myalgic Encephalomyelitis and chronic fatigue syndrome different illnesses? A preliminary analysis. Journal of Health Psychology 1–13 , 2014 - (Exclusion code:)</p> <p>– Jason, L., Richman, J. How Science Can Stigmatize: The Case of Chronic Fatigue Syndrome Journal of Chronic Fatigue Syndrome, Vol. 14(4),2007 (Exclusion code: not given)</p> <p>– Jason, L., Sunnquist, M., Brown, A. Evans, M., Vernon, S. Furst, J., Simonis, V. Examining case definition criteria for chronic fatigue syndrome and myalgic encephalomyelitis, Fatigue: Biomedicine, Health & Behavior, Jan 2014. DOI: (Exclusion code: 7)</p> <p>– Kennedy, G., Abbot, N., Spence, V. Underwood, C., Belch, J. The Specificity of</p>	

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		<p>the CDC-1994 Criteria for Chronic Fatigue Syndrome: Comparison Of Health Status in Three Groups of Patients Who Fulfill the Criteria AEP Vol. 14, No. 2 February 2004: 95–100 (Exclusion code: not given)</p> <p>– Jason, L., Richman, J., Friedberg, F., Wagner, L., Taylor, R., Jordan, K. Politics science and the emergence of a new disease. September 1997, American Psychologist. Vol. 52, No. 9, 973-983 (Exclusion code: not given)</p> <p>– Jason, L.A., Skendrovic, B., Furst, J., Brown, A., Weng, A., & Bronikowski, C. (2012). Data mining: Comparing the Empiric CFS to the Canadian ME/CFS case definition. Journal of Clinical Psychology. 68, 41-49. (Exclusion code: not given)</p> <p>Van Hoof E, De Meirleir K. Chronic Fatigue Syndrome and Myalgic Encephalomyelitis: Are Both Conditions on the Same Continuum? N Am J Psychol. 2005;7(2): 189-204.</p> <p>Jason LA, Evans M, Brown A, et al. Sensitivity and specificity of the CDC empirical chronic fatigue syndrome case definition. Psychology. 2010;1(1): 9-16. PMID: 23685416.</p> <p>Jason LA, Evans M, Brown A, et al. Sensitivity and specificity of the CDC empirical chronic fatigue syndrome case definition. Psychology. 2010;1(1): 9-16. PMID: 23685416.</p> <p>Relevant studies include</p> <p>This paper was included but only for comparing definitions</p> <p>– Brown, Abigail, Jason, Leonard. Validating a measure of myalgic encephalomyelitis/chronic fatigue syndrome symptomatology. Center for Community Research, DePaul University, Chicago, USA (Received 9 January 2014; accepted 22 May 2014 (Exclusion code: none given)</p> <p>– Samuel P. Watson, Amy S. Ruskin, Valerie Simonis, Leonard A. Jason, Madison Sunnquist, and Jacob D. Furst, "Identifying Defining Aspects of Chronic Fatigue Syndrome via Unsupervised Machine Learning and Feature Selection," International Journal of Machine Learning and Computing vol.4, no. 2, pp. 133-138, 2014. (Exclusion code: not given)</p> <p>Samuel P. Watson, Amy S. Ruskin, Valerie Simonis, Leonard A. Jason, Madison Sunnquist, and Jacob D. Furst, "Identifying Defining Aspects of Chronic Fatigue Syndrome via Unsupervised Machine Learning and Feature Selection," International Journal of Machine Learning and Computing vol.4, no. 2, pp. 133-138, 2014</p> <p>Bou-Holaigah I, Rowe PC, Kan J, et al. The relationship between neurally mediated hypotension and the chronic fatigue syndrome. JAMA. 1995;274(12):961-7. PMID: 7674527. (Exclusion code: 12)</p> <p>Excluded CPET studies</p> <p>– VanNess JM, Stevens SR, Bateman L, Stiles TL, Snell CR. "Post-exertional malaise in women with chronic fatigue syndrome." J Womens Health (Larchmt). 2010 Feb;19(2):239-44. (Exclusion code: none provided)</p>	

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		<p>– Vermeulen, R. Kurk, Visser, F. Sluiter, W. Scholte, H. Patients with chronic fatigue syndrome performed worse than controls in a controlled repeated exercise study despite a normal oxidative phosphorylation capacity. <i>J Transl Med</i>, 2010. 8: p. 93 (Exclusion code: none provided)</p> <p>– Kennedy G, Spence VA, McLaren M, et al. Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms. <i>Free Radic Biol Med</i>. 2005;39(5):584-9. PMID: 16085177. (Exclusion code: 2)</p> <p>Spinal Proteomes</p> <p>– Steven E Schutzer, Thomas E Angel, Tao Liu, Athena A Schepmoes, Therese R Clauss, Joshua N Adkins, David G Camp, Bart K Holland, Jonas Bergquist, Patricia K Coyle, Richard D Smith, Brian A Fallon, Benjamin H Natelson. Distinct Cerebrospinal Fluid Proteomes Differentiate Post-Treatment Lyme Disease from Chronic Fatigue Syndrome. <i>PLoS ONE</i>, 23 Feb 2011 DOI: (Exclusion code : Not given)</p> <p>Cognitive Functioning</p> <p>– Togo F, Lange G, Natelson BH, Quigley KS. Attention network test: Assessment of cognitive function in chronic fatigue syndrome. <i>J Neuropsychol</i>. 2013 Sep 24. PMID: 24112872 (Exclusion code: Not given)</p> <p>– Constant EL, Adam S, Gillain B, Lambert M, Masquelier E, Seron X. Cognitive deficits in patients with chronic fatigue syndrome compared to those with major depressive disorder and healthy controls. <i>Clin Neurol Neurosurg</i>. 2011 Jan 19. PMID: 21255911 (Exclusive code: Not given)</p> <p>– Demettre E, Bastide L, D'Haese A, De Smet K, De Meirleir K, Tiev KP, Englebienne P, Lebleu B. Ribonuclease L proteolysis in peripheral blood mononuclear cells of chronic fatigue syndrome patients. <i>J Biol Chem</i>. 2002 Sep 20;277(38):35746-51. PMID: 12118002 (Exclusive code: Not given)</p> <p>Autonomic</p> <p>– Allen J, Murray A, Di Maria C, Newton JL. Chronic fatigue syndrome and impaired peripheral pulse characteristics on orthostasis--a new potential diagnostic biomarker. <i>Physiol Meas</i>. 2012 Feb;33(2):231-41. PMID: 22273713 (Exclusive code: Not given)</p> <p>– Bou-Holaigah I, Rowe PC, Kan J, et al. The relationship between neurally mediated hypotension and the chronic fatigue syndrome. <i>JAMA</i>. 1995;274(12):961-7. PMID: 7674527. (Exclusion code: 12)</p> <p>– Frith J, Zalewski P, Klawe JJ, et al. Impaired blood pressure variability in chronic fatigue syndrome--a potential biomarker. <i>QJM</i>. 2012;105(9):831-8. PMID: 22670061. (Exclusion code: 8)</p> <p>– Ghosh AK, Ghosh K. The head-up tilt test for diagnosing chronic fatigue syndrome. <i>Qjm</i>. 2003;96(5):379-80. PMID: 12702788. (Exclusion code: 9)</p> <p>– Naschitz JE, Rosner I, Rozenbaum M, et al. The head-up tilt test with haemodynamic instability score in diagnosing chronic fatigue syndrome. <i>Qjm</i>.</p>	

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		2003;96(2):133-42. PMID: 12589011. (Exclusion code: 3) – Naschitz JE, Sabo E, Dreyfuss D, et al. The head-up tilt test in the diagnosis and management of chronic fatigue syndrome. <i>Isr Med Assoc J.</i> 2003;5(11):807-11. PMID: 14650107. (Exclusion code: 3) – Newton JL, Sheth A, Shin J, et al. Lower ambulatory blood pressure in chronic fatigue syndrome. <i>Psychosom Med.</i> 2009;71(3):361-5. PMID: 19297309. (Exclusion code: 12) – Naschitz JE, Rosner I, Rozenbaum M, et al. The capnography head-up tilt test for evaluation of chronic fatigue syndrome. <i>Semin Arthritis Rheum.</i> 2000;30(2):79-86. PMID: 11071579. Exclusion code: 3	
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Dimmock et al.	References	[1] Natelson BH, Cheu J, Hill N, et al. Single-blind, placebo phase-in trial of two escalating doses of selegiline in the chronic fatigue syndrome. <i>Neuropsychobiology.</i> 1998;37(3): 150-4. PMID: 9597672.	Inadequate duration (<12 weeks).
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Dimmock et al.	References	[1] Jason L, Muldowney K, Torres-Harding S. The Energy Envelope Theory and myalgic encephalomyelitis/chronic fatigue syndrome. [Erratum appears in AAOHN J. 2008 Jul;56(7): 288 Note: Muldowney, Kathleen [added]; Torres-Harding, Susan [added]. AAOHN J. 2008;56(5): 189-95. PMID: 18578185.	Wrong outcome, not evidence.
Dimmock et al.	References	[1] Lerner AM, Beqaj SH, Deeter RG, et al. A six-month trial of valacyclovir in the Epstein-Barr virus subset of chronic fatigue syndrome: improvement in left ventricular function. <i>Drugs Today</i> . 2002;38(8): 549-61. PMID: 12582420.	Wrong outcome, not evidence.
Dimmock et al.	References	[1] Martin RWY, Ogston SA, Evans JR. Effects of vitamin and mineral supplementation on symptoms associated with chronic fatigue syndrome with Coxsackie B antibodies. <i>J Nutr Med</i> . 1994;4(1): 11-23.	Wrong outcome, not evidence.
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Dimmock et al.	References	[1] Lerner AM, Beqaj SH, Deeter RG, et al. A six-month trial of valacyclovir in the Epstein-Barr virus subset of chronic fatigue syndrome: improvement in left ventricular function. <i>Drugs Today</i> . 2002;38(8): 549-61. PMID: 12582420.	Wrong outcome, not evidence.
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Dimmock et al.	References	[1] Nunez M, Fernandez-Sola J, Nunez E, et al. Health-related quality of life in patients with chronic fatigue syndrome: group cognitive behavioural therapy and graded exercise versus usual treatment. A randomized controlled trial with 1 year of follow-up. <i>Clin Rheumatol</i> . 2011;30(3): 381-9. PMID: 21234629.	Included paper.
Dimmock et al.	References	[1] Brurberg KG, Fonhus MS, Larun L, et al. Case definitions for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): a systematic review. <i>BMJ Open</i> . 2014;4(2): 2003973. PMID: 24508851.	Non-systematic review.
Sten Helmfrid	References	1. Centers for Disease Control and Prevention (2010). "Chronic Fatigue Syndrome" [Downloaded 140706]. http://www.cdc.gov/cfs/symptoms/ .	Reviewed, included for background.
Sten Helmfrid	References	2. The World Health Organization (2010). "International Statistical Classification of Diseases and Related Health Problems 10th Revision" [Downloaded 140610]. http://apps.who.int/classifications/icd10/browse/2010/en#/G93.3 .	Background paper only, no data for evidence.
Sten Helmfrid	References	3. IACFS/ME (2014). "Primer for Clinical Practitioners" [Downloaded 140610]. http://www.iacfsme.org/LinkClick.aspx?fileticket=Pi0KeDlc2M%3d&tabid=509 .	Background paper only, no data for evidence.
Sten Helmfrid	References	4. P.D. White et al. (2011). Comparison of adaptive pacing therapy, cognitive behavior therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomized trial. <i>Lancet</i> , vol. 377, pp. 611–90.	Included paper.
Sten Helmfrid	References	5. M. Williams (2009). "Statement of Concern about CBT/GET provided for the High Court Judicial Review of February 2009" [Downloaded 140706]. http://www.investinme.org/Article-361%20Statements%20of%20Concern%20-%20CBT-GET%20JR%20Feb09.htm .	Wrong publication type (comment).
Sten Helmfrid	References	6. F.N.M. Twisk and M. Maes (2009). A review on cognitive behavioral therapy (CBT) and graded exercise therapy (GET) in myalgic encephalomyelitis (ME) / chronic fatigue syndrome (CFS): CBT/GET is not only ineffective and not evidence-based, but also potentially harmful for many patients with ME/CFS. <i>Neuroendocrinology Letters</i> , vol. 30, pp. 284–99.	Non-systematic review.
Sten Helmfrid	References	7. The ME Association (2011). "ME Association press statement about the results of the PACE study" [Downloaded 140706]. http://www.meassociation.org.uk/2011/02/me-association-press-statement-on-the-pace-trial-results/ .	Wrong publication type (press statement).
Sten Helmfrid	References	8. J.T. Mitchell (2011). The PACE trial in chronic fatigue syndrome. <i>The Lancet</i> , vol. 377, p. 1831.	Wrong publication type (letter).
Sten Helmfrid	References	9. B. Stouten, E.M. Goudsmit, and N. Riley (2011). The PACE trial in chronic fatigue syndrome. <i>The Lancet</i> , vol. 377, p. 1832–3.	Wrong publication type (letter).

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Commentator & Affiliation	Section	Comment	Response
Sten Helmfrid	References	10. T. Kindlon (2011). The PACE trial in chronic fatigue syndrome. <i>The Lancet</i> , vol. 377, p. 1833.	Wrong publication type (letter).
Sten Helmfrid	References	11. A. Chaudhuri (2001). Cognitive behavior therapy for chronic fatigue syndrome. <i>The Lancet</i> , vol. 358, p. 238.	Wrong publication type (letter).
Sten Helmfrid	References	12. R.C.W. Vermeulen, H.R. Scholte, and P.D. Bezemer (2001). Cognitive behavior therapy for chronic fatigue syndrome. <i>The Lancet</i> , vol. 358, p. 238.	Wrong publication type (letter).
Sten Helmfrid	References	13. J.F. Wiborg, H. Knoop, M. Stulemeijer, J.B. Prins, and G. Bleijenberg (2010). How does cognitive behaviour therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity. <i>Psychological Medicine</i> , vol. 40, pp. 1281–7.	Wrong study design.
Sten Helmfrid	References	14. H. Knoop, J.B. Prins, M. Stulemeijer, J.W. van der Meer, and G. Bleijenberg (2007). The effect of cognitive behaviour therapy for chronic fatigue syndrome on self-reported cognitive impairments and neuropsychological test performance. <i>Journal of Neurology, Neurosurgery & Psychiatry</i> , vol. 78, pp. 434–6.	Wrong outcomes.
Sten Helmfrid	References	15. S.L. Nijhof, G. Bleijenberg, C.S. Uiterwaal, J.L. Kimpen, and E.M. van de Putte (2012). Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. <i>Lancet</i> , vol. 379, pp. 1412–8.	Wrong population (adolescents).
Sten Helmfrid	References	18. G.P. Holmes et al. (1988). Chronic Fatigue Syndrome: A Working Case Definition. <i>Annals of Internal Medicine</i> , vol. 108, pp. 387–9.	One of the main case definitions, this is included in the report.
Sten Helmfrid	References	19. K. Fukuda, S.E. Straus, I. Hickie, M.C. Sharpe, J.G. Dobbins, and A. Komaroff (1994). The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Group. <i>Annals of Internal Medicine</i> , vol. 121, pp. 953–9.	One of the main case definitions, this is included in the report.
Sten Helmfrid	References	22. M. Sharpe et al. (1996). Cognitive behavior therapy for chronic fatigue syndrome: a randomized controlled trial. <i>British Medical Journal</i> , vol. 312, pp 22–6.	Wrong publication (comment).
Sten Helmfrid	References	23. J.B. Prins, G. Bleijenberg, E. Bazelmans, L.D. Elving, T.M. de Boo, J.L. Severens, G.J. van der Wilt, P. Spinhoven, and J.W.M. van der Meer (2001). Cognitive behaviour therapy for chronic fatigue syndrome: a multicenter randomized controlled trial. <i>The Lancet</i> , vol. 357, pp. 841–7.	Excluded for wrong population (used CDC criteria, but did not require 4 of 8 additional symptoms).
Sten Helmfrid	References	24. M. Núñez, J. Fernández-Solà, E. Núñez, J.M. Fernández-Huerta, T. Godás-Sieso, and E. Gomez-Gil (2011). Health-related quality of life in patients with chronic fatigue syndrome: group cognitive behavioural therapy and graded exercise versus usual treatment. A randomised controlled trial with 1 year of follow-up. <i>Clinical Rheumatology</i> , vol. 30, pp. 381–9.	Included paper.
Sten Helmfrid	References	25. L. Darbishire, P. Seed, and L. Ridsdale (2005). Predictors of outcome following treatment for chronic fatigue. <i>The British Journal of Psychiatry</i> , vol. 186, pp. 180–1.	Wrong population.

Commentator & Affiliation	Section	Comment	Response
Sten Helmfrid	References	26. D.A.J. Tyrrell (1994). Report from the National Task Force on Chronic Fatigue Syndrome (CFS), Post Viral Fatigue Syndrome (PVFS) and Myalgic Encephalomyelitis (ME). Westcare: Bristol.	Report, not evidence.
Sten Helmfrid	References	27. W.C. Reeves, A. Lloyd, S.D. Vernon, N. Klimas, L.A. Jason, G. Bleijenberg, B. Evengård, P.D. White, R. Nisenbaum, and E.R. Unger (2003). Identification of ambiguities in the 1994 chronic fatigue research case definition and recommendations for resolution. BioMed Central Health Services Research, vol. 3: 25.	Background paper only, no data for evidence.
Sten Helmfrid	References	30. J.M. VanNess (2014). "A Realistic Approach to Exercise and Rehabilitation in ME/CFS", in Exercise and ME/CFS: the evidence, at Bristol Watershed, February 5th, 2014 [Downloaded 140707]. https://www.youtube.com/watch?v=q_cnva7zyKM .	Not evidence.
Sten Helmfrid	References	31. A.R. Light, L. Bateman, D. Jo, R.W. Hughen, T.A. Vanhaisma, A.T. White, and K.C. Light (2011). Gene expression alterations at baseline following moderate exercise in patients with chronic fatigue syndrome and fibromyalgia syndrome. Journal of Internal Medicine, vol. 271, pp. 64–81.	Discussion paper only, no data for evidence.
Sten Helmfrid	References	32. P.D. White, K.E. Nye, A.J. Pinching, T.M. Yap, N. Power, V. Vleck, D.J. Bentley, J.M. Thomas, M. Buckland, and J.M. Parkin (2004). Immunological Changes After Both Exercise and Activity in Chronic Fatigue Syndrome: A Pilot Study. Journal of Chronic Fatigue Syndrome, vol. 12, pp. 51–66.	Wrong outcome.
Sten Helmfrid	References	33. T. Kindlon (2011). "Reporting of Harms Associated with Graded Exercise Therapy and Cognitive Behavioural Therapy in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome" [Downloaded 140529]. http://www.iacfsme.org/LinkClick.aspx?fileticket=Rd2tIJ0oHqk%3D& .	Non-systematic review.
Sten Helmfrid	References	34. G.J. Bringsli, A. Gilje, and B.K. Getz Wold (2013). "ME-syke i Norge – fortsatt bortgjemt?" [Downloaded 140526]. http://me-foreningen.com/meforeningen/innhold/div/2013/05/ME-foreningens-Brukerunders%C3%B8kelse-ME-syke-i-Norge-Fortsatt-bortgjemt-12-mai-2013.pdf .	Background paper only, no data for evidence.
Sten Helmfrid	References	35. The ME Association (2010). "Managing my M.E. What people with ME/CFS and their carers want from the UK's health and social services" [Downloaded 140529]. http://www.meassociation.org.uk/wp-content/uploads/2010/09/2010-survey-report-lo-res10.pdf .	Wrong publication type.
Sten Helmfrid	References	36. J. Spotila (2010). "Post-Exertional Malaise in Chronic Fatigue Syndrom" [Downloaded 140913]. http://solvecfs.org/wp-content/uploads/2013/10/pem-series.pdf .	Wrong publication type.
Sten Helmfrid	References	37. J.H.M.M. Vercoulen, C.M.A. Swanink, J.M.D. Galama, J.F.M. Fennis, P.H.J. Jongen, O.R. Hommes, J.W.M. Van Der Meer, and G. Bleijenberg (1998). The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: Development of a model. Journal of Psychosomatic Research, vol. 45, pp. 507–17.	Reviewed, not evidence.

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Commentator & Affiliation	Section	Comment	Response
Sten Helmfrid	References	38. T.N. Beran and C. Violato (2010). Structural equation modeling in medical research: a primer. <i>BioMed Central Research Notes</i> , vol. 3: 267.	Reviewed, not evidence.
Sten Helmfrid	References	39. S. Song and L.A. Jason (2005). A population-based study of chronic fatigue syndrome (CFS) experienced in differing patient groups: An effort to replicate Vercoulen et al.'s model of CFS. <i>Journal of Mental Health</i> , vol. 14, pp. 277–89.	Reviewed, not evidence.
Sten Helmfrid	References	40. S.B. Harvey and S. Wessely (2009). Chronic fatigue syndrome: identifying zebras amongst the horses. <i>BioMed Central Medicine</i> , vol. 7: 58.	Reviewed, not evidence.
Anonymous	References	Wiborg JF, Knoop H, Stulemeijer M, Prins JB, Bleijenberg G. How does cognitive behavior therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity. <i>Psychol Med</i> . 2010 Aug;40(8):1281-7. PMID: 20047707. http://www.ncbi.nlm.nih.gov/pubmed/20047707	Wrong study design.
Anonymous	References	However, when reading the 2011 Lancet paper (see below URL) there appears to be 53/641 (8.3%) formal withdrawals and an additional 32/641 (5.0%) lost to followup. It is unclear how the figure of 1.7% was calculated. http://www.thelancet.com/journals/lancet/article/PIIS0140673611600962/images?imgId=gr1&sectionType=red	Re-reviewed and corrected.
Anonymous	References	Many of the pre-defined outcomes in the PACE Trial protocol (URL below) have been greatly altered or have not been published: http://www.biomedcentral.com/1471-2377/7/6	Noted, not evidence.
Malcolm Hopper	References	Detailed analyses of the many failings of the PACE trial -- with full references -- can be found at http://www.meactionuk.org.uk/magical-medicine.htm and at http://www.meactionuk.org.uk/COMPLAINT-to-Lancet-re-PACE.htm and at http://www.meactionuk.org.uk/Normal-fatigue.htm and at www.investinme.org/Article435StatisticsandME.htm	Reviewed, not evidence
Malcolm Hopper	References	In November 2006 senior Parliamentarians found Professor White's close financial involvement with the insurance industry "to be an area for serious concern and recommends a full investigation by the appropriate standards body" (http://erythos.com/gibsonenquiry/Docs/ME_Inquiry_Report.pdf).	Noted.
Malcolm Hopper	References	Another Principal Investigator in the PACE trial, Professor Michael Sharpe, is also deeply involved with the permanent health insurance industry, especially with UNUMProvident, whose track record is disturbing (see "The advent of UNUMProvident into the UK benefits system" http://www.meactionuk.org.uk/magical-medicine.htm). Professor Sharpe is known for his recommendation to insurers that claimants with ME/CFS should be subject to covert video surveillance.	Noted.
Malcolm Hopper	References	It appears that the Investigators likewise failed to observe necessary principles of good research required by the GMC "Good practice in research and Consent to research" (http://www.gmc-uk.org/static/documents/content/Research_guidance_FINAL.pdf)	Noted.

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Malcolm Hopper	References	The results of the 6MWT are significant and cannot be explained away as the Investigators have attempted to do by claiming that: “recovery from chronic fatigue syndrome (CFS), which is defined by a patient’s reported symptoms, is arguably best measured by multiple patient-reported outcome measures, rather than a single performance test” (http://www.meassociation.org.uk/2013/07/pace-trial-letters-and-reply-journal-of-psychological-medicine-august-2013/).	Noted.
Malcolm Hopper	References	When it was pointed out by the Medical Advisor to the ME Association in a letter to Psychological Medicine that such figures would have constituted a useful measurement of recovery, Professor Peter White attempted to defend this failure: “follow-up at six months after the end of therapy may be too short a period to affect either benefits or employment. We therefore disagree with Shepherd that such outcomes constitute a useful component of recovery in the PACE trial” (http://www.meassociation.org.uk/2013/07/pace-trial-letters-and-reply-journal-of-psychological-medicine-august-2013/).	Noted.
Malcolm Hopper	References	A “principal complaint of fatigue” is not ME/CFS (a classified neurological disorder in ICD-10 at G93.3), yet the Investigators stated in The Lancet: “The PACE findings can be generalised to patients who also meet alternative diagnostic criteria for chronic fatigue syndrome and myalgic encephalomyelitis” (The Lancet: February 18, 2011: DOI:10.1016/S0140-6736(11)60096-2).	Noted.
Malcolm Hopper	References	For individual references, see: (i) www.meactionuk.org.uk/Organic_evidence_for_Gibson.htm and (ii) www.meactionuk.org.uk/What_the_Experts_say_about_ME.htm).	Wrong publication type.
Malcolm Hopper	References	On 2nd July 2013 Professor Holgate addressed the Forward ME Group in the House of Lords; he called for radical change in ME/CFS research and said some researchers new to the field had been shocked by the poor quality of much ME/CFS research; he commented that some individuals had “made a career” out of ME/CFS theories that could be shaky and it was clear that this had to change (http://www.meassociation.org.uk/?p=16383).	Noted.
Malcolm Hopper	References	The emanations from the Science Media Centre (SMC) may be accepted by informed observers to be suspect because it represents only one narrow section of the scientific community (http://ngin.tripod.com/020602c.htm) but its wildly exaggerated press briefing for the PACE trial on 17th February 2011 was a travesty par excellence.	Noted.
Sister Sandra Duma, OSF, MS Ed	References	Volume 3 Issue 3 of the journal Biology 10.3390/biology3030606 contains an article by David Maughan and Michael Toth entitled “Discerning Primary and Secondary Factors Responsible for Clinical Fatigue in Multisystem Diseases” published on September 22, 2014. These are researchers from the Department of Molecular Physiology and Biophysics from the University of Vermont, Burlington, VT. The article’s abstract states the following:	Reviewed, not evidence.

Commentator & Affiliation	Section	Comment	Response
Sister Sandra Duma, OSF, MS Ed	References	7. Holmes, G.P.; Kaplan, J.E.; Gantz, N.M.; Komaroff, A.L.; Schonberger, L.B.; Straus, S.E.; Jones, J.F.; Dubois, R.E.; Cunningham-Rundles, C.; Pahwa, S.; et al. Chronic fatigue syndrome: A working case definition. <i>Ann. Intern. Med.</i> 1988, 108, 387–389, doi:10.7326/0003-4819-108-3-387.	This is one of the case definitions, it is included in the report.
Sister Sandra Duma, OSF, MS Ed	References	8. Morris, G.; Maes, M. A neuro-immune model of Myalgic Encephalomyelitis/Chronic fatigue syndrome. <i>Metab. Brain Dis.</i> 2013, 28, 523–540, doi:10.1007/s11011-012-9324-8.	Wrong outcomes.
Sister Sandra Duma, OSF, MS Ed	References	9. Morris, G.; Maes, M. Myalgic encephalomyelitis/chronic fatigue syndrome and encephalomyelitis disseminata/multiple sclerosis show remarkable levels of similarity in phenomenology and neuroimmune characteristics. <i>BMC Med.</i> 2013, 11, 205, doi:10.1186/1741-7015-11-205.	Wrong outcomes.
Sister Sandra Duma, OSF, MS Ed	References	10. Bierl, C.; Nisenbaum, R.; Hoaglin, D.C.; Randall, B.; Jones, A.B.; Unger, E.R.; Reeves, W.C. Regional distribution of fatiguing illnesses in the United States: A pilot study. <i>Popul. Health Metr.</i> 2004, 2, 1, doi:10.1186/1478-7954-2-1.	Wrong publication type.
Sister Sandra Duma, OSF, MS Ed	References	11. Sommer, C.; Hauser, W.; Burgmer, M.; Engelhardt, R.; Gerhold, K.; Petzke, F.; Schmidt-Wilcke, T.; Spath, M.; Tolle, T.; Uceyler, N.; et al. Etiology and pathophysiology of fibromyalgia syndrome. <i>Schmerz</i> 2012, 26, 259–267, doi:10.1007/s00482-012-1174-0.	Wrong outcome.
Sister Sandra Duma, OSF, MS Ed	References	12. Klimas, N.G.; Koneru, A.O. Chronic fatigue syndrome: Inflammation, immune function, and neuroendocrine interactions. <i>Curr. Rheumatol. Rep.</i> 2007, 9, 482–487, doi:10.1007/s11926-007-0078-y.	Background paper only, no data for evidence.
Sister Sandra Duma, OSF, MS Ed	References	13. Barnden, L.R.; Crouch, B.; Kwiatak, R.; Burnet, R.; Mernone, A.; Chryssidis, S.; Scroop, G.; Del Fante, P. A brain MRI study of chronic fatigue syndrome: Evidence of brainstem dysfunction and altered homeostasis. <i>NMR Biomed.</i> 2011, 24, 1302–1312, doi:10.1002/nbm.1692.	Wrong outcome.
Sister Sandra Duma, OSF, MS Ed	References	14. Pall, M.L. Elevated, sustained peroxynitrite levels as the cause of chronic fatigue syndrome. <i>Med. Hypotheses</i> 2000, 54, 115–125, doi:10.1054/mehy.1998.0825.	Wrong outcome.
Sister Sandra Duma, OSF, MS Ed	References	15. Pall, M.L. Novel Disease Paradigm Produces Explanations for a Whole Group of Illnesses; Washington State University: Pullman, WA, USA, 2009.	Reviewed, not evidence.
Sister Sandra Duma, OSF, MS Ed	References	16. Booth, N.E.; Myhill, S.; McLaren-Howard, J. Mitochondrial dysfunction and the pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). <i>Int. J. Clin. Exp. Med.</i> 2012, 5, 208.	Background paper only, no data for evidence.
Sister Sandra Duma, OSF, MS Ed	References	17. Myhill, S.; Booth, N.E.; McLaren-Howard, J. Targeting mitochondrial dysfunction in the treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) - a clinical audit. <i>Int. J. Clin. Exp. Med.</i> 2013, 6, 1–15.	Reviewed, not evidence.
Sister Sandra Duma, OSF, MS Ed	References	18. Morris, G.; Maes, M. Increased nuclear factor-kappaB and loss of p53 are key mechanisms in Myalgic Encephalomyelitis/chronic fatigue syndrome (ME/CFS). <i>Med. Hypotheses</i> 2012, 79, 607–613, doi:10.1016/j.mehy.2012.07.034.	Wrong outcomes.

Commentator & Affiliation	Section	Comment	Response
Sister Sandra Duma, OSF, MS Ed	References	19. Carlson, B.E.; Vigoreaux, J.O.; Maughan, D.W. Diffusion coefficients of endogenous cytosolic proteins from rabbit skinned muscle fibers. <i>Biophys. J.</i> 2014, 106, 780–792, doi:10.1016/j.bpj.2013.12.044.	Wrong population (rabbits).
Sister Sandra Duma, OSF, MS Ed	References	20. Massie, B.M.; Conway, M.; Rajagopalan, B.; Yonge, R.; Frostick, S.; Ledingham, J.; Sleight, P.; Radda, G. Skeletal muscle metabolism during exercise under ischemic conditions in congestive heart failure: Evidence for abnormalities unrelated to blood flow. <i>Circulation</i> 1988, 78, 320–326, doi:10.1161/01.CIR.78.2.320.	Wrong population (congestive heart failure).
Sister Sandra Duma, OSF, MS Ed	References	21. Newton, D.J.; Kennedy, G.; Chan, K.K.; Lang, C.C.; Belch, J.J.; Khan, F. Large and small artery endothelial dysfunction in chronic fatigue syndrome. <i>Int. J. Cardiol.</i> 2012, 154, 335–336, doi:10.1016/j.ijcard.2011.10.030.	Wrong outcomes.
Sister Sandra Duma, OSF, MS Ed	References	22. Lemle, M.D. Hypothesis: Chronic fatigue syndrome is caused by dysregulation of hydrogen sulfide metabolism. <i>Med. Hypotheses</i> 2009, 72, 108–109, doi:10.1016/j.mehy.2008.08.003.	Wrong publication type.
Sister Sandra Duma, OSF, MS Ed	References	23. Kobayashi, Y.M.; Rader, E.P.; Crawford, R.W.; Iyengar, N.K.; Thedens, D.R.; Faulkner, J.A.; Parikh, S.V.; Weiss, R.M.; Chamberlain, J.S.; Moore, S.A.; et al. Sarcolemma-localized nNOS is required to maintain activity after mild exercise. <i>Nature</i> 2008, 456, 511–515, doi:10.1038/nature07414.	Reviewed, not evidence.
Sister Sandra Duma, OSF, MS Ed	References	24. Lane, R.J.; Barrett, M.C.; Taylor, D.J.; Kemp, G.J.; Lodi, R. Heterogeneity in chronic fatigue syndrome: Evidence from magnetic resonance spectroscopy of muscle. <i>Neuromuscul. Disord.</i> 1998, 8, 204–209, doi:10.1016/S0960-8966(98)00021-2.	Reviewed, not evidence.
Sister Sandra Duma, OSF, MS Ed	References	25. Wong, R.; Lopaschuk, G.; Zhu, G.; Walker, D.; Catellier, D.; Burton, D.; Teo, K.; Collins-Nakai, R.; Montague, T. Skeletal muscle metabolism in the chronic fatigue syndrome. In vivo assessment by ³¹ P nuclear magnetic resonance spectroscopy. <i>Chest</i> 1992, 102, 1716–1722.	Reviewed, not evidence.
Sister Sandra Duma, OSF, MS Ed	References	26. McCully, K.K.; Natelson, B.H.; Iotti, S.; Sisto, S.; Leigh, J.S., Jr. Reduced oxidative muscle metabolism in chronic fatigue syndrome. <i>Muscle Nerve</i> 1996, 19, 621–625, doi:10.1002/(SICI)1097-4598(199605)19:5<621::AID-MUS10>3.0.CO;2-Q.	Reviewed, not evidence.
Sister Sandra Duma, OSF, MS Ed	References	27. Connolly, S.; Smith, D.G.; Doyle, D.; Fowler, C.J. Chronic fatigue: Electromyographic and neuropathological evaluation. <i>J. Neuro</i> 1993, 240, 435–438.	Reviewed, not evidence.
Sister Sandra Duma, OSF, MS Ed	References	28. Fulle, S.; Belia, S.; Vecchiet, J.; Morabito, C.; Vecchiet, L.; Fano, G. Modification of the functional capacity of sarcoplasmic reticulum membranes in patients suffering from chronic fatigue syndrome. <i>Neuromuscul. Disord.</i> 2003, 13, 479–484, doi:10.1016/S0960-8966(03)00042-7.	Reviewed, not evidence.
Sister Sandra Duma, OSF, MS Ed	References	29. Light, A.R.; Bateman, L.; Jo, D.; Hughen, R.W.; Vanhaitsma, T.A.; White, A.T.; Light, K.C. Gene expression alterations at baseline and following moderate exercise in patients with Chronic Fatigue Syndrome and Fibromyalgia Syndrome. <i>J. Intern. Med.</i> 2012, 271, 64–81, doi:10.1111/j.1365-2796.2011.02405.x.	Reviewed, not evidence.

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Commentator & Affiliation	Section	Comment	Response
Sister Sandra Duma, OSF, MS Ed	References	30. Light, A.R.; White, A.T.; Huguen, R.W.; Light, K.C. Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects. <i>J. Pain</i> 2009, 10, 1099–1112, doi:10.1016/j.jpain.2009.06.003.	Reviewed, not evidence.
Sister Sandra Duma, OSF, MS Ed	References	31. Pall, M.L. Chronic fatigue syndrome/myalgic encephalitis. <i>Br. J. Gen. Pract.</i> 2002, 52, 762; author reply 763–764.	Wrong publication type (comment).
Sister Sandra Duma, OSF, MS Ed	References	32. Shor, S. Pathogenesis of Chronic Fatigue Syndrome, a Multisystem Hypothesis. <i>J. Chronic Fatigue Syndr.</i> 2003, 11, 51–68, doi:10.1300/J092v11n03_05.	Reviewed, not evidence.
Sister Sandra Duma, OSF, MS Ed	References	33. McCully, K.K.; Natelson, B.H. Impaired oxygen delivery to muscle in chronic fatigue syndrome. <i>Clin. Sci. (Lond)</i> 1999, 97, 603–608; discussion 611–613.	Reviewed, not evidence.
Sister Sandra Duma, OSF, MS Ed	References	34. McCully, K.K.; Smith, S.; Rajaei, S.; Leigh, J.S., Jr.; Natelson, B.H. Muscle metabolism with blood flow restriction in chronic fatigue syndrome. <i>J. Appl. Physiol.</i> (1985) 2004, 96, 871–878, doi:10.1152/jappphysiol.00141.2003.	Reviewed, not evidence.
Parekh	References	1: Hyde BM, Goldstein J, Levine P. "The Clinical and Scientific Basis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome". The Nightingale Research Foundation, Ottawa, Canada, 1992. p 83	Background papers only, no data for evidence.
Parekh	References	2: Hyde, BM. "The Nightingale Definition of Myalgic Encephalomyelitis (ME)." The Nightingale Research Foundation, Ottawa, Canada, 2007.	Background papers only, no data for evidence.
Parekh	References	4: Dowsett EG, Goudsmit E, Macintyre A, Shepherd CB. "Report from The National Task Force on Chronic Fatigue Syndrome (CFS), Post Viral Fatigue Syndrome (PVFS), Myalgic Encephalomyelitis (ME)." Westcare, 1994. pp. 96-98.	Background papers only, no data for evidence.
Parekh	References	5: Goudsmit EM, Shepherd, C, Dancey P, and Howes S. "ME: Chronic fatigue syndrome or a Distinct Clinical Entity?", <i>Health Psychology Update</i> , 18 (2009), 26–31.	Background papers only, no data for evidence.

Commentator & Affiliation	Section	Comment	Response
Michelle Strausbaugh	References	<p>1 Charles Shepherd, "PACE trial: ME Association letter to 'The Lancet', 3 March 2011" ME Association website http://www.meassociation.org.uk/2011/03/pace-trialme-association-letter-to-the-lancet-3-march-2011/ (accessed Oct. 19, 2014)</p> <p>2 Johan WS Vlaeyen et. al "The PACE trial in chronic fatigue syndrome," The Lancet, Volume 377, Issue 9780, p1834, 28 May 2011 doi:10.1016/S0140-6736(11)60682-X3T. Jock Murray, Multiple Sclerosis: the History of a Disease (Demos: New York, 2005).</p> <p>4 a few examples of this discussion can be seen at "Chronic Fatigue Syndrome: CDC and NIH Research Activities Are Diverse, but Agency Coordination is Limited" GAO report to Senator Harry Reid June 2000 Craig Maupin "Scientific Review, CFS, and the NIH -- The CFS Special Emphasis Panel" at The CFS Report http://www.cfidsreport.com/Articles/NIH/NIH_CFS_3.htm Cort Johnson "Unfulfilled Commitments/Broken Promises: The NIH and Chronic Fatigue Syndrome After Twenty-Five Years" at Health Rising http://www.cortjohnson.org/blog/2013/12/22/unfulfilled-commitments-brokenpromises-nih-chronic-fatigue-syndrome-twenty-five-years/Mindy Kitei "Candid Conversation with Dr. Ian Lipkin" at CFS Central http://www.cfscentral.com/2014/05/candid-conversation-with-dr-ianlipkin.html Lipkin, a renowned pathologist, is quoted as saying: "I have been in competition now twice to get funded, and the people there who reviewed me gave me abysmal scores. And the critiques of my work were unfair, and one of the people who critiqued my work said, in fact, that this is a psychosomatic illness. I was floored. I protested, and for reasons that are obscure to me this same individual wound up back on the study section, and I got a similar unfundable score. Am I upset about this? Absolutely."</p> <p>5 Roberto Hernandez "Discrimination" in Sana Loue et. al. Encyclopedia of Women's Health (Kluwer Academic/Plenum Publishers: New York, 2004) p.223</p>	Reviewed, not evidence.
Lisa Petrison	References	Buchwald D, Cheney PR, Peterson DL, Henry B, Wormsley SB, Geiger A, Ablashi DV, Salahuddin SZ, Saxinger C, Biddle R, et al. A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpesvirus type 6 infection. Ann Intern Med. 1992 Jan 15;116(2):103-13. PMID: 1309285	Reviewed, not evidence.
Marry Dimmock	References	[1] PACE trial - Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. The Lancet - 5 March 2011 (Vol. 377, Issue 9768, Pages 823-836) http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext .	Included paper.

Commentator & Affiliation	Section	Comment	Response
Marry Dimmock	References	– The PACE trial, done in patients that met the Oxford definition, tested cognitive behavioral therapy (CBT) and graded exercise therapy (GET) which were used “on the basis of the fear avoidance theory of chronic fatigue syndrome” that “assume that the syndrome is perpetuated by reversible physiological changes of deconditioning and avoidance of activity.”	Noted.
Marry Dimmock	References	– PACE trial CBT Manual - http://www.pacetrials.org/docs/cbt-therapist-manual.pdf Page 81 - “It is important to include the precipitating factors, e.g., illness, life-events, working excessively hard, perfectionist personality etc. It is also important to discuss the maintaining factors, e.g., erratic or reduced activities, disturbed sleep patterns, unhelpful illness beliefs and any other unhelpful cognitions etc.	Manual for CBT in PACE trial, not evidence.
Marry Dimmock	References	[1] Borrell-Carrió, F., Suchman, A., Epstein, R. The Biopsychosocial Model 25 Years Later: Principles, Practice, and Scientific Inquiry. <i>Ann Fam Med</i> 2004;2:576-582. DOI: 10.1370/afm.245.	Reviewed, not evidence.
Marry Dimmock	References	[1] The following two articles discuss this theory. The work of Wessely is referred to as the biopsychosocial approach where the work of Vercoulen was described by Maes as a psychosocial approach.	Noted.
Marry Dimmock	References	· Harvey, S. Wessely, S. Chronic fatigue syndrome: identifying zebras amongst the horses <i>BMC Med.</i> 2009; 7: 58. Published online Oct 12, 2009. doi: 10.1186/1741-7015-7-58 PMID: PMC2766380. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2766380/	Reviewed, not evidence.
Marry Dimmock	References	· Vercoulen JH, Swanink CM, Galama JM, Fennis JF, Jongen PJ, Hommes OR, van der Meer JW, Bleijenberg G. The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: development of a model. <i>J Psychosom Res.</i> 1998;45:507–517. doi: 10.1016/S0022-3999(98)00023-3.	Background paper only, no data for evidence.
Marry Dimmock	References	[1] Examples include the following:	Noted.
Marry Dimmock	References	· Certain English institutions and government agencies have incorrectly stated that the term “CFS” is classified not only as a neurological disorder but also as neurasthenia. In the 2001 British WHO Guide to Mental Health in Primary Care, adapted from the WHO’s guide to mental health in primary care, England placed CFS not only in the neurological chapter but also under neurasthenia in the mental and behavioral disorders chapter. In 2001 and again in 2004, WHO staff issued a ruling that the placement under neurasthenia was incorrect.	Noted.
Marry Dimmock	References	· Summary of statement by World Health Organization about the dual classification http://www.theoneclickgroup.co.uk/documents/ME-CFS_docs/WHO%20STATEMENT.doc	Reviewed, not evidence.
Marry Dimmock	References	“Andre L’Hours, the Technical Officer at the WHO headquarters in Geneva who is responsible for the ICD, confirmed that it was “unacceptable” if the same disorder had been included in two places in the ICD-10 and that the same disorder could not be differently categorised under the one WHO banner.”	Noted.

Commentator & Affiliation	Section	Comment	Response
Marry Dimmock	References	· WHO Guide to Mental Health In Primary Care” published by the WHO collaborating Center at Kings College. It is not clear exactly when this was first published but it is on the 2001 version of this page. http://web.archive.org/web/20010709061548/http://cebhm.warne.ox.ac.uk/cebhm/whoguidemhpcuk/disorders/f48-0.html	Report, not evidence.
Marry Dimmock	References	· The Read Codes, used as standard terminology in clinical practice in England, classifies CFS (and ME which is listed as a synonym of CFS) as both a neurological disorder and as a form of neurasthenia listed under somatoform disorders in the mental health disorders section.[1]	Noted.
Marry Dimmock	References	o Read Codes http://systems.hscic.gov.uk/data/uktc/readcodes	Reviewed, not evidence.
Marry Dimmock	References	o Read Codes, Clinical Terms Version 3 (CTV3) can be seen here http://bioportal.bioontology.org/ontologies/RCD?p=classes&conceptid=http%3A%2F%2Fpurl.bioontology.org%2Fontology%2FRCD%2FXa01F	Reviewed, not evidence
Marry Dimmock	References	· The SNOMED CT clinical terminology system, important to the implementation of electronic health records, lists CFS as a multisystem disorder but also as a mental disorder. ME is listed as a synonym of CFS and thus similarly classified	Noted.
Marry Dimmock	References	o http://www.ihtsdo.org/snomed-ct/	Reviewed, not evidence.
Marry Dimmock	References	o Multiple browsers are available, including: http://bioportal.bioontology.org/ontologies/SNOMEDCT?p=classes&conceptid=http%3A%2F%2Fpurl.bioontology.org%2Fontology%2FSNOMEDCT%2F52702003	Reviewed, not evidence.
Marry Dimmock	References	· Training Module for Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME) - Guidelines for the Disability Analyst. Continuing Medical Education Programme Provided On Behalf Of The Department For Work And Pensions. MED/S2/CMEP~0017 Version 7 Final Module: 6. May 28, 2014. http://www.actionforme.org.uk/Resources/Action%20for%20ME/dwp-training-doc-for-assessors-on-me.pdf	Reviewed, not evidence.
Marry Dimmock	References	o In 2014, the U.K. Department of Work and Pensions issued a training module for “CFS/ME” disability assessment,[1] which also incorrectly states that the ICD-10 classifies the disease as both neurasthenia and a neurological disorder. But the manual goes further and explicitly links CFS/ME to the term “somatic symptom disorder” in the new version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The manual states that somatic symptom disorder is a newer term for somatoform disorder.	Noted.
Marry Dimmock	References	· Treatments for Fibromyalgia in Adult Subgroups. Agency for Healthcare Research and Quality. Draft July 23, 2014. Page 30 of file, page 4 of second section http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayProduct&productID=1944 The July 23, 2014 draft evidence review for	Reviewed, not applicable to this evidence review.
Marry Dimmock	References	o Treatment for Fibromyalgia in Adult Subgroups,[1] published by AHRQ, referred to CFS as a “functional somatic syndrome”, a term widely equated to the terms “somatoform illness” and “somatic symptom disorder.”	Noted

Commentator & Affiliation	Section	Comment	Response
Marry Dimmock	References	[1] Examples of CFS being referred to as Somatorm illness.	Noted.
Marry Dimmock	References	Overview - Slide presentation [PDF format] Somatoform disorders – functional somatic syndromes – Bodily distress syndrome. Need for care and organisation of care in an international perspective – EACLPP Lecture, Prof. Per Fink, MD, Ph.D, Dr.Med.Sc. www.functionaldisorders.dk	Wrong publication type.
Marry Dimmock	References	Michael B. First, M.D., DSM Somatic Presentations of Mental Disorders (September 6-8, 2006). American Psychiatric Association. http://www.dsm5.org/Research/Pages/SomaticPresentationsofMentalDisorders%28September6-8,2006%29.aspx	Reviewed, not evidence.
Marry Dimmock	References	[1] Sykes, R. Physical or mental? A perspective on chronic fatigue syndrome. <i>Advances in Psychiatric Treatment</i> 2002, 8:351-358. DOI: 10.1192/apt.8.5.351	Reviewed, not evidence.
Public Reviewer # 49	References	http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0017287	Reviewed, not evidence.
Anonymous	References	Bennet R. n.d. The concurrence of lupus and fibromyalgia: implications for diagnosis and management. http://www.myalgia.com/concurrence_of_lupus_and_fibromy.htm	Reviewed, not evidence.
Anonymous	References	Blitshteyn S. Letter. Postural tachycardia syndrome and anxiety disorders. <i>J Neurol Neurosurg Psychiatry</i> . Published 8 April 2009. http://jnnp.bmj.com/content/80/3/339/reply#jnnp_el_4620	Wrong publication type (letter).
Anonymous	References	Ellen. (2012) Migraine Triggers and Comorbidities: Autoimmune Disease. http://migraine.com/blog/triggers-and-comorbidities-autoimmune-disease/	Wrong publication type (letter).
Anonymous	References	Henderson T. 2014 interview with Cort Johnson. http://simmaronresearch.com/2014/09/treatment-resistant-depression-chronic-fatigue-syndrome-child-psychiatrist-finds-success-antivirals/	Wrong publication type (opinion).
Anonymous	References	Invest in ME (liME). 2014 research colloquium. http://www.investinme.org/Documents/Education/Invest%20in%20ME%20BRME%20C4%20and%20IIMEC9%20Report%202014.pdf	Wrong publication type (Conference proceedings).
Anonymous	References	Jerant A. 2014 Interview with Red Orbit. http://www.redorbit.com/news/health/1113247938/depression-questionnaires-not-always-enough-100214/	Wrong publication type (interview, opinion).
Anonymous	References	McGrath S. (2013) A Dozen Different Diseases? Stephen Holgate calls for Radical Change in ME/CFS Research. http://phoenixrising.me/archives/18222	Wrong publication type (opinion).
Anonymous	References	Molderings GJ, Brettner S, Homann J, Afrin LB. Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. <i>J Hematol Oncol</i> . 2011; 4: 10. PMC3069946	Reviewed, not evidence.
Anonymous	References	Raj SJ, Rowe PC. (2014) Connecting the Dots between EDS and POTS. http://www.prweb.com/releases/2014/10/prweb12209300.htm [ME/CFS is mentioned as a side note]	Reviewed, not evidence.

Commentator & Affiliation	Section	Comment	Response
Anonymous	References	Ray A, Oriss TB, Wenzel SE. Emerging Molecular Phenotypes of Asthma. Am J Physiol Lung Cell Mol Physiol. 2014 Oct 17. pii: ajplung.00070.2014. [Epub ahead of print]	Reviewed, not evidence
Anonymous	References	Lee YJ, Park KS. Irritable bowel syndrome: Emerging paradigm in pathophysiology. World J Gastroenterol. Mar 14, 2014; 20(10): 2456–2469.	Reviewed, not evidence.
Anonymous	References	Stein, E. (2005) 'Clinical Guidelines for Psychiatrists: Assessment and Treatment of Patients with ME/CFS'. http://www.mecfs.org.au/media/resources/Article-ESteinPsychiatricCFSGuideline05.pdf	Reviewed, not evidence.
Anonymous	References	Underhill R et al. Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: Primer for Clinical Practitioners, 2014 Ed. http://www.iacfsme.org/Home/Primer/tabid/509/Default.aspx	Background paper only, no data for evidence.
Anonymous	References	Voinov B, Richie WD, Bailey RK. Depression and Chronic Diseases: It Is Time for a Synergistic Mental Health and Primary Care Approach. Prim Care Companion CNS Disord. 2013; 15(2): PCC.12r01468. PMC3733529	Reviewed, not evidence.
Public Reviewer # 51	References	(Fluge O, Bruland O, Risa K, et al. Benefit from B-lymphocyte depletion using the antiCD20 antibody rituximab in chronic fatigue syndrome. A double-blind and placebo-controlled study. PLoS ONE. 2011;6(10):e26358. PMID: 22039471), was excluded b	Inadequate duration (<12 weeks). Included in discussion.
Public Reviewer # 51	References	The Voice of the Patient report issued by the FDA in 2013	Reviewed for background.
Public Reviewer # 51	References	The National CFIDS Foundation “In Memoriam” list of people with ME/CFS that have died	Noted.
Public Reviewer # 51	References	Immunological abnormalities as potential biomarkers in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis.	Background paper only, no data for evidence.
Public Reviewer # 51	References	Brenu EW1, van Driel ML, Staines DR, Ashton KJ, Ramos SB, Keane J, Klimas NG, Marshall-Gradsnik SM.	Background paper only, no data for evidence.
Public Reviewer # 51	References	J Transl Med. 2011 May 28;9:81. doi: 10.1186/1479-5876-9-81.	Background paper only, no data for evidence.
Public Reviewer # 51	References	Markers of inflammation and immune activation in chronic fatigue and chronic fatigue syndrome.	Background paper only, no data for evidence.
Public Reviewer # 51	References	Buchwald D1, Wener MH, Pearlman T, Kith P.	Background paper only, no data for evidence.
Public Reviewer # 51	References	J Rheumatol. 1997 Feb;24(2):372-6.	Background paper only, no data for evidence.
Public Reviewer # 51	References	Brain 5-HT1A receptor binding in chronic fatigue syndrome measured using positron emission tomography and [11C]WAY-100635.	Background paper only, no data for evidence.
Public Reviewer # 51	References	Cleare AJ1, Messa C, Rabiner EA, Grasby PM.	Background paper only, no data for evidence.
Public Reviewer # 51	References	Biol Psychiatry. 2005 Feb 1;57(3):239-46.	Background paper only, no data for evidence.

Source: <http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2004>
Published Online: December 9, 2014

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 51	References	Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome.	Background paper only, no data for evidence.
Public Reviewer # 51	References	Demitrack MA1, Dale JK, Straus SE, Laue L, Listwak SJ, Kruesi MJ, Chrousos GP, Gold PW.	Background paper only, no data for evidence.
Public Reviewer # 51	References	J Clin Endocrinol Metab. 1991 Dec;73(6):1224-34	Background paper only, no data for evidence.
Public Reviewer # 51	References	Impaired cardiac function in chronic fatigue syndrome measured using magnetic resonance cardiac tagging.	Background paper only, no data for evidence.
Public Reviewer # 51	References	Hollingsworth KG1, Hodgson T, Macgowan GA, Blamire AM, Newton JL.	Background paper only, no data for evidence.
Public Reviewer # 51	References	J Intern Med. 2012 Mar;271(3):264-70. doi: 10.1111/j.1365-2796.2011.02429.x. Epub 2011 Aug 15.	Background paper only, no data for evidence.
Public Reviewer # 51	References	Gene expression subtypes in patients with chronic fatigue syndrome/myalgic encephalomyelitis.	Background paper only, no data for evidence.
Public Reviewer # 51	References	Kerr JR1, Petty R, Burke B, Gough J, Fear D, Sinclair LI, Matthey DL, Richards SC, Montgomery J, Baldwin DA, Kellam P, Harrison TJ, Griffin GE, Main J, Enlander D, Nutt DJ, Holgate ST.	Background paper only, no data for evidence.
Public Reviewer # 51	References	J Infect Dis. 2008 Apr 15;197(8):1171-84. doi: 10.1086/533453.	Background paper only, no data for evidence.
Public Reviewer # 51	References	Snell CR1, Stevens SR, Davenport TE, Van Ness JM.	Background paper only, no data for evidence.
Public Reviewer # 51	References	Phys Ther. 2013 Nov;93(11):1484-92. doi: 10.2522/ptj.20110368. Epub 2013 Jun 27	Background paper only, no data for evidence.
Public Reviewer # 51	References	Loss of capacity to recover from acidosis on repeat exercise in chronic fatigue syndrome: a case-control study.	Wrong study design.
Public Reviewer # 51	References	Jones DE1, Hollingsworth KG, Jakovljevic DG, Fattakhova G, Pairman J, Blamire AM, Trenell MI, Newton JL.	Wrong study design.
Public Reviewer # 51	References	Eur J Clin Invest. 2012 Feb;42(2):186-94. doi: 10.1111/j.1365-2362.2011.02567.x. Epub 2011 Jul 12.	Wrong study design.
Public Reviewer # 51	References	Influence of exhaustive treadmill exercise on cognitive functioning in chronic fatigue syndrome.	Wrong study design.
Public Reviewer # 51	References	LaManca JJ1, Sisto SA, DeLuca J, Johnson SK, Lange G, Pareja J, Cook S, Natelson BH	Wrong study design.
Public Reviewer # 51	References	Am J Med. 1998 Sep 28;105(3A):59S-65S	Wrong study design.
Public Reviewer # 51	References	Fluge O, Bruland O, Risa K, et al. Benefit from B-lymphocyte depletion using the antiCD20 antibody rituximab in chronic fatigue syndrome. A double-blind and placebo-controlled study. PLoS ONE. 2011;6(10):e26358. PMID: 22039471	Inadequate duration (<12 weeks).

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 51	References	J Behav Neurosci Res. 2010 Jun 1;8(2):1-8. A Comparison of Immune Functionality in Viral versus Non-Viral CFS Subtypes. Porter N1, Lerch A2, Jason LA, Sorenson M, Fletcher MA, Herrington J.	Reviewed, not evidence.
Public Reviewer # 51	References	Cytokine expression profiles of immune imbalance in post-mononucleosis chronic fatigue. Broderick G, Katz BZ, Fernandes H, Fletcher MA, Klimas N, Smith FA, O'Gorman MR, Vernon SD, Taylor R. J Transl Med. 2012 Sep 13;10:191. doi: 10.1186/1479-5876-10-191.	Background paper only, no data for evidence.
Public Reviewer # 51	References	Exercise responsive genes measured in peripheral blood of women with chronic fatigue syndrome and matched control subjects. Whistler T, Jones JF, Unger ER, Vernon SD.	Background paper only, no data for evidence.
Public Reviewer # 51	References	A Chronic Fatigue Syndrome – related proteome in human cerebrospinal fluid. Baraniuk JN, Casado B, Maibach H, Clauw DJ, Pannell LK, Hess S S. BMC Neurol. 2005 Dec 1;5:22.	Background paper only, no data for evidence.
Public Reviewer # 51	References	Differences in metabolite-detecting, adrenergic, and immune gene expression after moderate exercise in patients with chronic fatigue syndrome, patients with multiple sclerosis, and healthy controls. White AT, Light AR, Hughen RW, Vanhaitsma TA, Light KC.	Background paper only, no data for evidence.
Public Reviewer # 51	References	Genetics and Gene Expression Involving Stress and Distress Pathways in Fibromyalgia with and without Comorbid Chronic Fatigue Syndrome. Light KC, White AT, Tadler S, Iacob E, Light AR.	Reviewed, not evidence.
Public Reviewer # 51	References	Severity of symptom flare after moderate exercise is linked to cytokine activity in chronic fatigue syndrome. White AT, Light AR, Hughen RW, Bateman L, Martins TB, Hill HR, Light KC.	Reviewed, not evidence.
Public Reviewer # 51	References	Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects. Light AR, White AT, Hughen RW, Light KC. Psychosom Med. 2012 Jan;74(1):46-54. doi: 10.1097/PSY.0b013e31824152ed. Epub 2011 Dec 30.	Reviewed, not evidence.
Public Reviewer # 51	References	Cerebral vascular control is associated with skeletal muscle pH in chronic fatigue syndrome patients both at rest and during dynamic stimulation. He J, Hollingsworth KG, Newton JL, Blamire AM.	Reviewed, not evidence.
Public Reviewer # 51	References	Clinical characteristics of a novel subgroup of chronic fatigue syndrome patients with postural orthostatic tachycardia syndrome. Lewis I, Pairman J, Spickett G, Newton JL.	Discussion paper only, no data for evidence.
Public Reviewer # 51	References	Chronic fatigue syndrome and impaired peripheral pulse characteristics on orthostasis—a new potential diagnostic biomarker. Allen J, Murray A, Di Maria C, Newton JL.	Discussion paper only, no data for evidence.
Public Reviewer # 51	References	Increased d-lactic Acid intestinal bacteria in patients with chronic fatigue syndrome. Sheedy JR, Wettenhall RE, Scanlon D, Gooley PR, Lewis DP, McGregor N, Stapleton DI, Butt HL, DE Meirleir KL. In Vivo. 2009 Jul-Aug;23(4):621-8.	Background paper only, no data for evidence.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 51	References	Responses to exercise differ for chronic fatigue syndrome patients with fibromyalgia. Cook DB, Stegner AJ, Nagelkirk PR, Meyer JD, Togo F, Natelson BH. Med Sci Sports Exerc. 2012 Jun;44(6):1186-93. doi: 10.1249/MSS.0b013e3182417b9a.	Wrong publication type (letter).
Public Reviewer # 51	References	Med Sci Sports Exerc. 2005 Sep;37(9):1460-7. Exercise and cognitive performance in chronic fatigue syndrome. Cook DB1, Nagelkirk PR, Peckerman A, Poluri A, Mores J, Natelson BH.	Background paper only, no data for evidence.
Public Reviewer # 51	References	Regional grey and white matter volumetric changes in myalgic encephalomyelitis (chronic fatigue syndrome): a voxel-based morphometry 3 T MRI study. Puri BK1, Jakeman PM, Agour M, Gunatilake KD, Fernando KA, Gurusinghe AI, Treasaden IH, Waldman AD, Gishen P.	Reviewed, not evidence.
Public Reviewer # 51	References	Unravelling intracellular immune dysfunctions in chronic fatigue syndrome: interactions between protein kinase R activity, RNase L cleavage and elastase activity, and their clinical relevance. Meeus M, Nijs J, McGregor N, Meeusen R, De Schutter G, Truijien S, Frémont M, Van Hoof E, De Meirleir K. In Vivo. 2008 Jan-Feb;22(1):115-21.	Reviewed, not evidence.
Public Reviewer # 51	References	Detection of herpesviruses and parvovirus B19 in gastric and intestinal mucosa of chronic fatigue syndrome patients. Frémont M, Metzger K, Rady H, Hulstaert J, De Meirleir K. In Vivo. 2009 Mar-Apr;23(2):209-13.	Reviewed, not evidence.
Public Reviewer # 51	References	J Psychosom Res. 2006 Jun;60(6):559-66. Impaired natural immunity, cognitive dysfunction, and physical symptoms in patients with chronic fatigue syndrome: preliminary evidence for a subgroup? Siegel SD1, Antoni MH, Fletcher MA, Maher K, Segota MC, Klimas N.	Background paper only, no data for evidence.
Public Reviewer # 51	References	Neuroimage. 2005 Jul 1;26(3):777-81. Epub 2005 Apr 7. Gray matter volume reduction in the chronic fatigue syndrome. de Lange FP1, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, Toni I.	Reviewed, not evidence.
Public Reviewer # 51	References	Neuroimage. 2005 Jun;26(2):513-24. Epub 2005 Apr 7. Objective evidence of cognitive complaints in Chronic Fatigue Syndrome: a BOLD fMRI study of verbal working memory. Lange G1, Steffener J, Cook DB, Bly BM, Christodoulou C, Liu WC, Deluca J, Natelson BH. Appl Neuropsychol. 2001;8(1):23-30.	Discussion paper only, no data for evidence.
Public Reviewer # 51	References	Quantitative assessment of cerebral ventricular volumes in chronic fatigue syndrome. Lange G1, Holodny AI, DeLuca J, Lee HJ, Yan XH, Steffener J, Natelson BH. PLoS One. 2011 Feb 23;6(2):e17287. doi: 10.1371/journal.pone.0017287.	Background paper only, no data for evidence.
Public Reviewer # 51	References	Distinct cerebrospinal fluid proteomes differentiate post-treatment lyme disease from chronic fatigue syndrome. Schutzer SE1, Angel TE, Liu T, Schepmoes AA, Clauss TR, Adkins JN, Camp DG, Holland BK, Bergquist J, Coyle PK, Smith RD, Fallon BA, Natelson BH.	Reviewed, not evidence.

Commentator & Affiliation	Section	Comment	Response
Anonymous	References	Also, while this report is in French, a review of Belgium CFS clinic providing biopsychosocial rehabilitative approaches is available here: http://www.inami.fgov.be/care/fr/revalidatie/general-information/studies/study-sfc-cvs/index.htm As	Reviewed, not evidence.
Anonymous	References	[1] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1371151/	Reviewed, not evidence.
Anonymous	References	[2] http://www.amjmed.com/article/0002-9343%2893%2990183-P/abstract	Wrong intervention.
Anonymous	References	[3] http://www.amjmed.com/article/S0002-9343%2899%2980332-5/abstract	Wrong publication type.
Anonymous	References	[4] http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2800%2904198-2/abstract	Excluded.
Anonymous	References	[5] http://www.ncbi.nlm.nih.gov/pubmed/15585538	Excluded for wrong population (used CDC criteria, but did not require 4 of 8 additional symptoms).
Anonymous	References	[6] http://www.ncbi.nlm.nih.gov/pubmed/18827302	Included paper.
Anonymous	References	[7] http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=7826378&fileId=S0033291709992212	Wrong publication type.
Anonymous	References	[8] http://www.ncbi.nlm.nih.gov/pubmed/21334061	Included paper.
Anonymous	References	[9] http://www.biomedcentral.com/1471-2377/7/6/comments#306608	Wrong publication type (protocol only, no evidence).
Anonymous	References	[10] http://www.ncbi.nlm.nih.gov/pubmed/17369597	Wrong outcomes.
Anonymous	References	[11] http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0040808	Wrong outcome.
Anonymous	References	[12] http://qjmed.oxfordjournals.org/content/early/2013/03/28/qjmed.hct061.full	Wrong study design.
Anonymous	References	[13] http://www.biomedcentral.com/1471-2377/7/6	Wrong publication type (protocol only, no evidence).
Anonymous	References	[14] http://www.bmj.com/content/340/bmj.c1777	Included paper.
Anonymous	References	[15] http://www.fine-trial.net/downloads/CFS%20patient%20presentation.pdf	Wrong publication type (report only, no evidence).
Anonymous	References	[16] http://www.ncbi.nlm.nih.gov/pubmed/22192566	Wrong outcome.
Anonymous	References	[17] http://psychologyatmanchester.edublogs.org/2013/08/02/interview-with-prof-alison-wearden-by-as-level-work-experience-students/	Wrong publication type (interview).
Anonymous	References	[18] http://www.thecochranelibrary.com/details/editorial/6125601/From-observation-to-evidence-of-effectiveness-the-haphazard-route-to-finding-out.html	Wrong publication type.
Anonymous	References	[19] http://www.ncbi.nlm.nih.gov/pubmed/23363640	Included paper.
Anonymous	References	[20] http://jpubhealth.oxfordjournals.org/content/21/3/255.abstract	Paper on norming the SF-36. Reviewed for background information.
Anonymous	References	[21] Office of Population Censuses and Surveys. Social Survey Division, OPCS Omnibus Survey, November 1992. Colchester, Essex: UK Data Archive, September 1997. SN: 3660	Reviewed, not evidence.
Anonymous	References	[22] http://www.bmj.com/content/342/bmj.d1168	Wrong publication type.

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Anonymous	References	[23] http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2811%2960172-4/fulltext#article_upsell	Wrong publication type.
Anonymous	References	[24] http://www.biomedcentral.com/1472-6963/11/217	Background paper only, no data for evidence.
Anonymous	References	[25] http://www.thenakedscientists.com/HTML/content/news-archive/news/2384/	Wrong publication type.
Anonymous	References	[26] http://www.pacetrail.org/trialinfo	Wrong publication type.
Anonymous	References	[27] Bleijenberg G, Prins J, and Bazelmans E. 'CHAPTER 23: Cognitive-Behavioral Therapies' in 'Handbook of Chronic Fatigue Syndrome' 2003; John Wiley & Sons	Wrong publication type.
Anonymous	References	[28] http://www.swissre.com/clients/newsletters/Managing_claims_for_chronic_fatigue_the_active_way.html	Wrong publication type.
Anonymous	References	[29] http://www.theguardian.com/commentisfree/2008/mar/17/epluribusunum	Wrong publication type.
Anonymous	References	[30] http://disability-studies.leeds.ac.uk/files/library/A-Tale-of-two-Models-Leeds1.pdf	Wrong publication type.
Anonymous	References	[31] http://www.midmoors.co.uk/Unum/unum_in_uk.pdf	Wrong publication type.
Anonymous	References	[32] http://internationalgreensocialist.wordpress.com/illness-as-deviance-work-as-glittering-salvation-and-the-psyching-up-of-the-medical-model-strategies-for-getting-the-sick-back-to-work/	Wrong publication type.
Anonymous	References	[33] http://dpac.uk.net/2014/09/gordon-waddells-biopsychosocial-attack-on-disabled-people	Wrong publication type.
Anonymous	References	http://cfstreatment.blogspot.com/2014/09/theahrqdraftreportfundamentallyand.html#sthash.tZkIXvLH.dpuf	Wrong publication type.
Anonymous	References	http://www.occupycfs.com/2014/10/06/they-know-what-they-are-doing-not/	Reviewed, not evidence.
Public Reviewer # 43	References	http://www.sciencedirect.com/science/article/pii/S1043466614002919	Reviewed, abstract, wrong publication type.
Public Reviewer # 43	References	http://www.prohealth.com	Drug store website, not evidence,
Public Reviewer # 41	References	TEST 1 CardioPulmonary Exercise Testing with measurement of VO2 max anaerobic threshold and maximal heart rate and respiration. This test is mentioned in the book Disability and CFS Clinical Legal and Patient Perspectives with this comment by Dr. Daniel Peterson One objective and reproducible technique for determining and measuring functional disability that should be used consistently is CardioPulmonary Exercise Testing with measurement of VO2 max anaerobic threshold and maximal heart rate and respiration. The test is well established sedentary and ill norms are published and the technology is relatively inexpensive and quite available. Approximately 1700 patients as in 1997 have been tested over the past 10 years and the test is now used on the initial visit to screen patients to direct rehabilitation and adjunctively to determine disability. Diminished Cardiopulmonary Capacity During PostExertional Malaise Abstract J. Mark VanNess PhD Christopher R. Snell PhD Staci R.	Book does not provide evidence for report.

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		<p>StevensConclusion In the absence of a second exercise test the lack of any significant differences for the first test would appear to suggest no functional impairment in CFS patients. However the results from the second test indicate the presence of a CFS related postexertional malaise. It might be concluded then that a single exercise test is insufficient to demonstrate functional impairment in CFS patients. A second test may be necessary to document the atypical recovery response and protracted malaise unique to CFS.</p> <p>Legal and Scientific Considerations of the Exercise Stress Test Ciccolla Stevens Snell Van Ness 2007 The Haworth Press This article examines the legal and scientific basis on which an exercise stress test can provide medically acceptable evidence of disability for the CFS patient. This research groups excellent work proves the postexertional disability that ME CFS patients suffer much worse on average than heart failure and COPD patients.</p> <p>TEST 2 Brain neuro SPECT PET scans and MRI brain scan Evidence From 2007 IACFSM. E. conference New methods in viral studies using refined technology show further abnormalities in subsets of MECFS patients. Increased use of instruments like MRI SPECTSPET PET and fMRI show some of the abnormalities in functioning that patients with MECFS experience on a daily basis but these may not have practical application if a patient cannot have this testing done. A number of abnormalities with reduced responsiveness on fMRI is an essential feature of MECFS.</p> <p>Brain imaging shows that amongst other abnormalities MECFS patients have reduced blood flow to the brain especially to areas that are involved in autonomic nervous system functioning and in sleep concentration and pain including the prefrontal cortices the anterior cingulate and the cerebellum altered patterns of brain activation reduced grey matter volume altered serotonergic neurotransmission and reduced acetylcarnitine uptake.</p> <p>A collaboration of researchers from Spain Belgium and Australia used SPET scanning to observe patterns of brain activity they found that the brain abnormalities correlated with abnormal immune results. Patients with MECFS require more brain regions to perform tasks ie. they have to work harder to achieve the same results as healthy controls.</p> <p>One particular area of the brain the Wernicke area essential for understanding and formulating coherent speech showed evidence of reduced activity after exercise.</p> <p>Proton resonance spectroscopy showed greatly increased levels of brain metabolites lactate levels were 300 higher than in controls.</p> <p>According to Dr Tae Park from South Korea the unexplained bright spots on MRI scans of some MECFS patients are evidence of an arteriolar vasculopathy or a blood vessel disease. He believes MECFS is a systemic microvascular inflammatory process a process that would affect not only the brain or the heart or the muscles but potentially every organ system in the body. Dr Park found not only capillary inflammation and perivascular cuffing the accumulation of immune cells that surround injured blood vessels but that all the MECFS patients in his study demonstrated remarkably reduced renal blood flow.</p>	

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		<p>Dr Park noted that diabetics with renal vascular disease also complain of profound fatigue. Dr Hiro Kuratsune from Japan gave a summary of what is known about brain function in MECFS. It has been known for over a decade that frontal and temporal lobe blood flow is reduced in MECFS and that exercise exacerbates this reduced blood flow for up to 72 hours. The new evidence is that elevated elastase and RNaseL levels correlate with reduced blood flow. It is known that the MRI is abnormal in the majority of people with MECFS due to numerous T2 weighted hypertintense foci with evidence of demyelination. Patients with more brain abnormalities tend to be more physically impaired. The remarkable similarity in the brain images of patients with MECFS and multiple sclerosis was noted. Dr Gudrun Lange from New Jersey USA stated what can be said with certainty about the central nervous system findings in MECFS¹ the major cognitive problem seen is in information processing² studies showing reduced cerebral blood flow are starting to show consistency³ there is a problem with serotonergic neurotransmission in the hippocampus and anterior cingulate regions⁴ there are spinal fluid abnormalities⁵ fMRI studies are showing altered patterns of brain activation. See references at the end of this article for more Neuroimaging evidence for MECFS diagnosis.</p> <p>TEST 3 Mitochondrial Dysfunction</p> <p>The magnetic resonance spectroscopy MRS brain scan is a most informative of the brain scans for MECFS. It indicates mitochondrial dysfunction. Check www.cocure.com in the archives for more info on MRS and google Dr Cheneys MRS scan data for his patients. MRS scanning has found abnormally high lactic acid spikes near around the hippocampus in PWME brains which indicates mitochondrial dysfunction a central feature being found in just about all cases through the UKs BioLab testing. An MRI is good for ruling out gross abnormalities such as tumors and obvious areas of brain damage while the SPECT can help verify hypoperfusion in the brain. From 2007 IACFSM. E. Conference Dr Jonathan Kerr from London stated that his gene expression studies are finding three main abnormalities in MECFS patients these involve the immune system mitochondrial function and Gprotein signaling. There are seven genes upregulated in MECFS those associated with apoptosis pesticides mitochondrial function demyelination and viral binding sites. Kerr mentioned three genes in particular gelsolin which is involved in apoptosis and amyloidosis one that is upregulated by organophosphates and a mitochondrial gene involved in the demyelination of nerves. Also Mitochondrial abnormalities in the postviral fatigue syndrome. Behan WM More IA Behan PO Department of Pathology University of Glasgow Scotland. Acta Neuropathol 1991;83:1615 We have examined the muscle biopsies of 50 patients who had postviral fatigue syndrome PFS for from 1 to 17 years. We found mild to severe atrophy of type II fibres in 39 biopsies with a mild to moderate excess of lipid. On ultrastructural examination 35 of these specimens showed branching and fusion of mitochondrial cristae. Mitochondrial degeneration was obvious in 40 of the</p>	

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		<p>biopsies with swelling vacuolation myelin figures and secondary lysosomes. These abnormalities were in obvious contrast to control biopsies where even mild changes were rarely detected. The findings described here provide the first evidence that PFS may be due to a mitochondrial disorder precipitated by a virus infection. TEST 4 TH1TH2 imbalance TH1TH2 Cytokine Production Immune testing availability http://punevx.com Th1Th2 Imbalance There are two general branches Th1Th2 of the immune system. Some patients appear to have an over activation of the anti-inflammatory Th2 branch and an under activation of the pro-inflammatory Th1 branch of the immune system</p>	
Public Reviewer # 41	References	<p>Additional References Poor mans tilt table testing description Neuroimaging References Neurological Dysfunction in Chronic Fatigue Syndrome Journal of Chronic Fatigue Syndrome The Haworth Medical Press an imprint of The Haworth Press Inc. Vol. 6 No. 34 2000 pp. 5168. Abhijit Chaudhuri DM MD MRCP Peter O. Behan DSc MD FACP FRCPSPECT Imaging of the Brain Comparison of Findings in Patients with Chronic Fatigue Syndrome AIDS Dementia Complex and Major Unipolar Depression Richard B. Schwartz Anthony L. Komaroff Basem M. Garada Marcy Gleit Teresa H. Doolittle David W. Bates Russell G. Vasily B. Leonard Holman American Journal of Roentgenology Vol 162 943951 Copyright 1994 by American Roentgen Ray Society. Summary This study shows that CFS ME shares some similarities on SPECT imaging with AIDS Dementia Complex acute changes in radionuclide uptake in the younger population may be caused by inflammatory processes at the cellular or micro vascular level the findings in CFS ME face are consistent with the hypothesis that CFS ME ... results from a viral infection of neurons glia or vasculature viral infection can provoke neurological dysfunction by interfering with intracellular mechanisms or membrane transport systems or by cerebral hypoperfusion due to vasculitis. It has been known for some time that CFS patients have abnormal blood flow in their brains that is some areas of the brain are not getting as much blood as they should. Dr. Ismael Mena has studied M. E. CFS patients brains using SPECT scans at the University of California Los Angeles where he is a professor of radiology Ismael Mena M.D. Study of Cerebral Perfusion by NeuroSPECT in Patients with Chronic Fatigue Syndrome The Cambridge Symposium on Myalgic Encephalomyelitis 1990 1 2122. Gordon R et al. Cortical motor potential alterations in chronic fatigue syndrome. Int J Molec Med. 1999 4 49399. Proton magnetic resonance spectroscopy of basal ganglia in chronic fatigue syndrome. Chaudhuri A Condon BR Gow JW Brennan D Hadley DM. Neuroreport. 2003 Feb 10 1422258. Costa DC Brostoff J Douli V Eli PJ. Brainstem hypoperfusion in patients with Myalgic Encephalomyelitis Chronic Fatigue Syndrome. Eur J Nucl Med 1992 19 733. Brainstem perfusion is impaired in chronic fatigue syndrome. DC Costa C Tannock and J Brostoff. Quarterly Journal of Medicine December 1995 88 767-773 Relationship of brain MRI</p>	Wrong outcome.

Commentator & Affiliation	Section	Comment	Response
		<p>abnormalities and physical functional status in chronic fatigue syndrome Cook DB Natelson BH. Int J Neurosci 20001071216Brain positron emission tomography PET in chronic fatigue syndrome preliminary data Tirelli U et al. Am J Med 1998105 3A54S58SBrain MRI abnormalities exist in a subset of patients with chronic fatigue syndrome. Lange G DeLuca J Maldjian JA Lee H Tiersky LA Natelson BH. J Neurol Sci. 1999 Dec 1171137.Chronic fatigue syndromeaetiological aspects. Dickinson CJ. Eur J Clin Invest. 1997 Apr27425767Brain MR in chronic fatigue syndrome. Greco A Tannock C Brostoff J Costa DC. AJNR Am J Neuroradiol. 1997 Aug187 12659.Relationship of brain MRI abnormalities and physical functional status in chronic fatigue syndrome. Cook DB Lange G DeLuca J Natelson BH. Int J Neurosci. 2001 Mar1071216.Quantitative assessment of cerebral ventricular volumes in chronic fatigue syndrome. Lange G Holodny AI DeLuca J Lee HJ Yan XH Steffener J Natelson BH. Appl Neuropsychol. 2001812330.Immune Function ReferencesEvidence for the Presence of Immune Dysfunction in Chronic Fatigue Syndrome. Benjamin H. NatelsonMohammad H. Haghghiand Nicholas M. Ponzio. Departments of Neurosciences Pathology University of Medicine and DentistryNew Jersey Medical School Department of Psychology Rutgers University Newark New Jersey Clinical and Diagnostic Laboratory Immunology July 2002 p. 747752 Vol. 9 No. 4 1071412X0204.000 DOI 10.1128CDLI.9.4.747752.2002 2002 American Society for MicrobiologyLow NK syndrome and its relationship to chronic fatigue syndrome. Aoki T Miyakoshi H Usuda Y Herberman RB. Clinical Immunology and Immunopathology 1993 693 25365.A chronic illness characterized by fatigue neurologic and immunologic disorders and active human herpesvirus type 6 infection. Buchwald D Cheney PR Peterson DL Henry B Wormsley SB Geiger A Ablashi DV Salahuddin SZ Saxinger C Biddle R et al. Annals of Internal Medicine 1992 1162 10313. Immunologic abnormalities associated with chronic fatigue syndrome. Barker E Fujimura SF Fadem MB Landay AL Levy JA. Clinical Infectious Diseases 1994 18Supp 1 S13641. A comprehensive immunological analysis in chronic fatigue syndrome. Gupta S Vayuvegula B. Scandinavian Journal of Immunology 1991 33 319327. Abstract A detailed analysis of cellmediated and antibodymediated immunity was performed in 20 CDCdefined patients with chronic fatigue syndrome CFS and 20 age and sexmatched healthy controls. CD3 CD4 CD8 and CD20lymphocytes were comparable in two groups. Natural killer cells as defined by CD16 CD56 and CD57 antigens were significantly reduced in CFS. A significant increase in the proportions of CD4 ICAM 1 T cells was observed in CFS. Monocytes from CFS displayed increased density as determined by mean fluorescence channel numbers of intercellular adhesion molecule 1 ICAM1 and lymphocyte function associated antigen 1 LFA1 but showed decreased enhancing response to recombinant interferongamma in vitro. The lymphocyte</p>	

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		<p>DNA synthesis in response to phytohaemaglobulin PHA Concanavalin A Con A and pokeweed mitogen PWM was normal but the response to soluble antigens was significantly reduced. Serum IgM IgG IgA and IgG subclasses were normal. In vivo specific antibody response to pneumococcus vaccine was depressed in CFS. Forty percent of patients showed titres of antihuman herpes virus 6 antiHHV6 antibody higher than that in the controls greater than or equal to 180. These data suggest immunological dysfunction in patients with chronic fatigue syndrome. The significance of these observations is discussed. Immunological abnormalities in patients with chronic fatigue syndrome. Tirelli U Marotta G Improta S Pinto A.Scandinavian Journal of Immunology 1994 406 6018.Low NK syndrome and its relationship to chronic fatigue syndrome. Aoki T Miyakoshi H Usuda Y Herberman RB. Clinical Immunology and Immunopathology 1993 693 25365. Immunologic abnormalities associated with chronic fatigue syndrome. Barker E Fujimura SF Fadem MB Landay AL Levy JA. Clinical Infectious Diseases 1994 18Supp 1 S13641.Description of poor mans tilt table testing procedure courtesy of Dr. Mary SchweitzerYou lie still and rest for 15 minutes to 20 minutes. Then they take your blood pressure and pulse. Then you sit up for about10 minutes same thing. Then you stand and lean slightly against a wall do NOT flex your muscles or struggle or talk.Be calm. Have somebody there who can catch you if there is troubleAfter ten minutes they should do the blood pressure and pulse again.Keep leaning. DO NOT FLEX ANY MUSCLES OR TALK.After another ten minutes take them again.If at any time you start to feel sweaty or hot or nauseous or basically superM.E. they need to do the bp and pulse right away and get you lying down. Congratulations.For Neurally Mediated Hypotension NMH you have to have a 2025 mm drop in systolic blood pressure the higher number. If your pulse suddenly rises at least 30 bpm beats per minute then you have Postural Orthostatic Tachycardia Syndrome POTS. Dr. Rowe believes they are both really the same thing with either if you dont get down youre going to pass out. And the treatment for both is the same. Rowe published the first article on the relationship between CFS and autonomic nervous system dysfunction NMHPOTSin JAMA in the fall of 1995. Note See abstract below.What is neurally mediated hypotensionNeurally mediated hypotension is also known by the following names the fainting reflex neurocardiogenic syncope vasodepressor syncope the vasovagal reflex and autonomicdysfunction. Hypotension is the formal medical term for low bloo</p>	

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 13	References	<p>The studies that the reviewers included were not only too few they were completely inadequate to properly address the Key Questions. The Key Questions to be addressed by the report are as follows:</p> <ol style="list-style-type: none"> 1. What methods are available to clinicians to diagnose MECFS and how do the use of these methods vary by patient subgroups? 2. What are widely accepted diagnostic methods and what conditions are required to be ruled out or excluded before assigning a diagnosis of MECFS? 3. What is the accuracy and concordance of diagnostic methods? 4. What harms are associated with diagnosing MECFS? 5. What are the a) benefits and b) harms of therapeutic interventions for patients with MECFS and how do they vary by patient subgroups? 6. What are the characteristics of responders and nonresponders to interventions? <p>There are problems with the wording of some of these questions. For example in a country in which 80% of the physicians don't believe that CFS is a real disease what could widely accepted be referring to? And "What harms are associated with diagnosing MECFS" seems to have an a priori assumption that diagnosing the disease may in itself cause harm. But aside from the oddness of the wording the studies they chose do not adequately address the questions. The criteria for exclusion from the review included among others that the study did not last long enough (therapeutic trial of less than 12 weeks) was published before 1988, had wrong study design or did not address a Key Question. There were 8 more exclusions. From among the thousands of studies that have been conducted the criteria limited the review to a scant 64 studies. Some of the landmark studies that were excluded were all of the studies demonstrating immune dysfunction e.g. NK cell deficiency studies by Brenu et al. studies of viral reactivation and antiviral treatments e.g. all Lerner and Jessop studies, Kerr parvovirus B19 study, studies documenting brain abnormalities e.g. Langes MRI study and all of the papers published by Tom Kindlon on harms associated with GET and CBT. Not even appearing on the excluded list were the groundbreaking 2-day CPET studies conducted by Keller, Stevens and Snell, Peckermans cardiac insufficiency studies and the recent Watanabe study on CNS inflammation. The fact that some of the most significant studies in the MECFS literature did not even appear on the excluded list was mindboggling. Of the studies that appeared on the exclusion list the reasons given were various but among the most frequently cited were that the studies did not address the Key Questions. Yet several studies that directly addressed the Key Questions were omitted for example 2-Day CPET studies were not even considered while studies that did not directly address the Key Questions were included. This arbitrariness permeated the entire study selection process. See more at http://pcfstreatment.blogspot.com/2014/09/theahrqdraftreportfundamentallyand.html and ash.tzk1xvLH.dpuf</p>	Studies have been reviewed, but not evidence.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #57	References	I have been ill with ME for nearly 18 years following an infection with mononucleosis at age 24. For the first few years at doctors orders I forced myself to continue to work fulltime with extreme difficulty and also followed their mistaken directive of GET and CBT as treatments. As a result I had a massive setback that led me bedridden and I have remained so for nearly 14 years. I cannot stand walk fully bathe myself or speak more than a few words above a whisper. This is in large part due the the very treatments you describe as helpful. For more of my story please see my testimony to the CFS Advisory Committee which was presented in 2009 https://www.youtube.com/watch?v=LvweCk44WHs . Since I am too ill to write a lengthy reply I am sharing Public Reviewer # 39s public commentary instead which I agree with completely. Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome MECFS Raise Questions of the Reviews Fitness for Purpose by Public Reviewer # 39 S.E. http://bit.ly/1r1XWBt Thank you.	Reviewed, not evidence.
Michelle Strausbaugh	References	1 Charles Shepherd, "PACE trial: ME Association letter to 'The Lancet', 3 March 2011" ME Association website http://www.meassociation.org.uk/2011/03/pace-trial-me-association-letter-to-the-lancet-3-march-2011/ (accessed Oct. 19, 2014) 2 Johan WS Vlaeyen et. al "The PACE trial in chronic fatigue syndrome," The Lancet, Volume 377, Issue 9780, p1834, 28 May 2011 doi:10.1016/S0140-6736(11)60682-X 3 T. Jock Murray, Multiple Sclerosis: the History of a Disease (Demos: New York, 2005). 4 a few examples of this discussion can be seen at "Chronic Fatigue Syndrome: CDC and NIH Research Activities Are Diverse, but Agency Coordination is Limited" GAO report to Senator Harry Reid June 2000 Craig Maupin "Scientific Review, CFS, and the NIH -- The CFS Special Emphasis Panel" at The CFS	Wrong publication types and others provide no relevant evidence.
Public Reviewer # 41	References	http://www.nameus.org/MECFSExplainPagesTestAbnormalities.htm TOP 10 TESTS	Reviewed, not evidence.
Public Reviewer # 14	References	http://www.occupycfs.com/2014/10/06/they-know-what-they-are-doing-not	Reviewed, not evidence.
Peer Reviewer #1	General	Congratulations on this report. It does a good job showing the dismal lack of even basic research studies on ME/CFS. Clinical research studies on medications for relief of symptoms also need to be done.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General	The review is more useful for researchers and less useful for clinicians: It suffers from problems which are intrinsic to systematic reviews. It is of necessity, unable to include important information which is common knowledge among clinicians, experienced in treating patients with ME/CFS, but the information has never been formally studied. The review is thus biased towards studies which have been done. For instance your review studied harms associated with a diagnosis of ME/CFS, but you were not able to show the great relief of patients when they have been given a medical diagnosis of ME/CFS to explain their symptoms. A diagnosis enables the patient to learn more about the illness, educates family members, helps patients to co-operate better in treatment and enables them to join an appropriate support group. This has not been formally studied. I am concerned that your review will provide evidence which might encourage some clinicians to withhold an appropriate diagnosis of ME/CFS.	Thank you and we appreciate your comment on the potential positive effects from receiving a diagnosis of ME/CFS. We have highlighted this potential and indicated that we did not find any evidence that studied this outcome.
TEP Reviewer #1	General	The report seemed very thorough, and clearly written.	Thank you.
TEP Reviewer #2	General	This report represents an enormous amount of work to essentially reprise what has been stated and re-stated in prior literature reviews any number of times. So it's not clear to this reviewer that any new clinically meaningful information is revealed. The target population and audience are adequately defined. Key questions are explicitly stated, but they simply reiterate ongoing issues in the literature.	Thank you for your comments, they have been noted.
TEP Reviewer #2	General	On the other hand, if this report raises awareness about the illness and the substantial knowledge deficits that exist, that would be beneficial, particularly if it leads to new policy and funding initiatives. In that case, the report will have served a useful purpose.	Agree.
TEP Reviewer #2	General	Structure and organization of the report is good. Main points are clearly presented.	Thank you.
TEP Reviewer #3	General	Yes this report is very well organized and the clinical questions are very clearly stated.	Thank you.
TEP Reviewer #3	General	The section on interventions is well organized, clear and informative. The discussion on diagnostic markers could benefit from improvements discussed above. In the end, case definition and diagnostic measures require continued attention and further development by the research community.	Thank you. We have revised the diagnosis section to be more readable. We agree that diagnosis of ME/CFS is an area of focus for future research.
Peer Reviewer #2	General	Thank you for the opportunity to review this important document. The document is clinically meaningful and addresses clear key questions. The underlying search is well executed and described.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	This reviewer welcomes the AHRQ's initiative to conduct this systematic review, because systematic reviews can form the basis for identifying best clinical practices and establishing funding priorities for future research. Overall, my impression is that the review is well constructed and executed. This reviewer would welcome more emphasis on the importance of objective classification, such as by way of exercise testing, in order to compliment current nominal diagnostic classification schema. The use of exercise testing in this regard would allow for both differentiation between individuals with ME/CFS and other fatiguing health conditions, as well as provide objective evidence of ability/disability in the manner of functional classification.	Thank you - will include further under future research needs.
TEP Reviewer #4	General	I appreciate the careful review undertaken by AHRQ on this difficult to grasp topic and the opportunity to review the report.	Thank you.
TEP Reviewer #4	General	The report is not clinically meaningful. It will not guide clinicians toward improved diagnosis nor facilitate better treatment for patients.	Thank you for your comments; they have been noted.
TEP Reviewer #4	General	The target population is defined and key questions well stated.	Thank you.
David Egan	General	Dear Sir/Madam, I am an American citizen temporarily living in Ireland. I am contacting you in relation to your web page http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1906 which contains several serious errors and omissions. I have detailed them below ME/CFS is not a "constellation of symptoms, with post-exertional malaise and/or chronic and disabling fatigue being the hallmark." It is a physical biological illness, classified by the WHO as neurological, originating from a viral or other pathogen infection(s) and accompanying immune dysfunctions and subsequent neurological, endocrine, mitochondria and cardiac abnormalities, or in some cases or organophosphate or toxin poisoning which causes some of the aforementioned abnormalities. The post exertional malaise and disabling fatigue is a consequence of this, in a similar way to that encountered in Cancer, cardiac illnesses, diabetes, MS and other neurological illnesses.	We appreciate your opinion. It was not the intent of this report to review possible causes of ME/CFS but the literature thus far has not identified a unifying cause for this syndrome (set of symptoms).

Commentator & Affiliation	Section	Comment	Response
David Egan	General	<p>"The variable symptomatology and lack of an identifiable disease process with gold standard of measurement have challenged researchers and clinicians in their attempts to better understand the disease process and its effects on patients."</p> <p>This is the direct result of calling ME and CFS psychological illnesses. Most doctors and researchers have been told these lies for over 25 years ,and this belittling and mocking of the illness as psychological and "all in the mind" has resulted in very little or no government, academic and private funding for research into ME. The illness ME has been starved of research for 25 years. The NICE clinics in Britain forbid many biological tests to identify subgroup biomarkers for the illness. Patients and patient groups with their own personal funds have funded some biological research into ME, and a few governments have put a small amount of funding into biological n search over the years. From this have emerged some biological biomarkers for subgroups.</p> <p>A few biological biomarkers have been found for the illness, please view www.me-ireland.com/scientific.htm</p>	<p>Thank you for your comment. Reviewing the cause (etiology) of ME/CFS was beyond the scope of this report. We have included the biomarker studies that have been used in an attempt to diagnose ME/CFS.</p>
David Egan	General	<p>"Thus finding ways to accurately diagnose patients to optimize management has significant public health importance and consequences."</p> <p>Start doing biological tests and stop using the subjective and useless psychological tests. Then you will make some progress in the area of diagnostics and treatments. You could start here at http://www.me-ireland.com/structure.htm#8</p>	<p>The purpose of this report was to review methods used to diagnose ME/CFS, some of which are symptom-based subjective tools, and others are serum markers. We agree that there is a need for additional and improved testing measures.</p>
David Egan	General	<p>"Currently there are no U.S. Food and Drug Administration (FDA) approved medications for the treatment of ME/CFS"</p> <p>The FDA can fast track psychological and psychiatric treatments, and regularly ignores dangerous side effects when approving these new drugs and treatments. It breaks it's own rules. Using this logic, it should be able to fast track Ampligen and other biological treatments for the ME subgroups.</p>	<p>The role and function of the FDA is outside of the scope of this report and our authority.</p>
David Egan	General	<p>The Fukuda criteria 1994 do not describe ME or CFS. The criteria is vague and ambiguous, it is unscientific, un-medical, and could be describing any number of illnesses, biological or psychological. It lacks specificity and sensitivity. It deliberately omits important medical and scientific findings in 1994 and prior to 1994. The criteria actually describes nothing and was open to abuse and was abused. The letter by Dr.Straus to Dr. Fukuda clarifies these points http://www.me-ireland.com/straus/straus.htm</p> <p>The criteria led to premature patient deaths, see http://www.ncf-net.org/memorial.htm</p> <p>The Fukuda criteria needs to be declared null and void by the US Government and it's constituent agencies such as the DHHS,NIH,CDC and 10M.</p>	<p>We included all case definitions of ME/CFS to provide a broad view of the foundation of this literature.</p>

Commentator & Affiliation	Section	Comment	Response
David Egan	General	<p>The Key Questions</p> <ul style="list-style-type: none"> o What methods are available to clinicians to diagnose MIE/CFS and how do the use of these methods vary by patient subgroups? • What are widely accepted diagnostic methods and what conditions are required to be ruled out or excluded before assigning a diagnosis of ME/CFS? • What is the accuracy and concordance of diagnostic methods? • What harms are associated with diagnosing ME/CFS? o What are the (a) benefits and (b) harms of therapeutic interventions for patients with ME/CFS and how do they vary by patient subgroups? • What are the characteristics of responders and non-responders to interventions? " <p>The answer to the above is detailed on http://www.me-ireland.com/structure.htm#8 . These are based on medical and scientific facts dating back to 1955.</p>	<p>We have systematically reviewed the scientific evidence surrounding diagnosis and treatment of the syndrome of ME/CFS. We appreciate the value of patient advocacy groups and the support provided through websites. Our report follows a strict pre-defined methodology that directs the search and the selection of studies.</p>
Peer Reviewer # 4	General	<p>the GET results are superficial and meaningless, in fact the ill effect of GET was completely overlooked The CBT benefit were not analysed in a scientific manner, no Karnofsky scores were quoted in either case.</p> <p>The paper was written to substantiate a flawed CBT/ GET protocol that has been shown to be non effective in various critical assessments</p>	<p>We reported all available measures for included outcomes; they can be found in appendix J of the report. Outcomes were synthesized only when multiple studies used the same outcome measure for an intervention. Few studies reported Karnofsky scores for CBT or GET, but other outcome scales were used to pool this data. The aim of the report was to objectively present and synthesize the available body of evidence. Limitations of the included studies have been highlighted in the discussion.</p>
Peer Reviewer # 4	General	<p>Clarity and Usability: well structured and organized but wrongly interpreted. GET can have bad reaction in the study group</p>	<p>Thank you. We have expanded our discussion of the potential harms of GET and have added additional data from recent publications.</p>

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	General	This report is not clinically useful, as the authors themselves state in the Conclusions of the Structured Abstract: "No current diagnostic tool or method has been adequately tested to identify patients with ME/CFS when diagnostic uncertainty exists." Also on page ES-29 "The limitations in applicability as well as the limitations of the evidence base make it difficult to draw firm conclusions with implications for clinical practice." I completely agree with this statement. I do not agree, however, that the authors should highlight CBT and GET as showing "some" benefit. As the only positive statement in the abstract, this will be picked up by the media and exaggerated, and as discussed below, the statement is not warranted on the evidence. Few individuals, other than experts and concerned patients, will read anything more than the executive summary, and many will read only the abstract.	Your concerns about the presentation of the results have been noted. The executive summary and abstract have been edited to be more concise and clear.
Peer Reviewer #5	General	I cannot blame the authors for the many problems in this review; they were given an impossible task. My low rating of the report is not due to their lack of effort, but because of problems in study design. Indeed, this study must have been a frustrating nightmare to work on. The authors were expected to review the literature for an immature field that has suffered from three serious problems: the absence of an generally accepted definition of the syndrome, the fact that the illness has been psychologized, and the lack of adequate funding that would permit adequate subject numbers and replication or validation studies. However, the report does not adequately address the extent these problems. The report could be valuable if the impact of the problems on the field were highlighted. Surely the authors must be appalled at the current state of research and clinical knowledge in this field. This is not due to the quality of the researchers and clinicians who have produced approximately 5000 papers, but due to the aforementioned issues. The target population is not well defined, because that is one of the major issues concerning the illness. Different definitions have been used to identify patients and subjects for studies. Some of these definitions are rather non-specific (a glaring example is the Oxford definition), which therefore undoubtedly results in some individuals who are actually clinically depressed being included in the subject population. The authors decided not to address this issue and decided to include studies that used any of the definitions that have variously been described in the literature. If individuals who are actually have primary depression are included in a study, positive results of psychological treatment such as CBT are likely to be overstated.	Thank you for your comments. We appreciate that the case definitions are very different and that some are more inclusive than others and may reflect less severe cases or non-cases of ME/CFS as is outlined in the Key Question 1 results in the report. After consultation with our working group and Technical Expert Panel, we did elect to include all case definitions in the report a priori for several reasons. First, there are very few trials and excluding some of these definitions would limit the evidence even further than is already outlined. Second, the intent was that this could at least provide a foundation to determine what interventions may be effective. Where available, we compared findings using different case definitions to determine if findings were consistent or not across studies. We have expanded the future research needs discussion to indicate that future studies should perform sensitivity analysis to determine differences between case definitions as well as subgroups of patients that meet different criteria.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	General	At present the only widely accepted diagnostic methods are the presence of a list of symptoms, which varies according to the definition. What conditions are required to be ruled out depends on what definition is used; some require the absence of some other illness that could cause fatigue, though this is problematic given that individuals with ME/CFS have a greater chance of developing depression than the healthy population. By deciding to use studies with any of the definitions, the authors avoid answering this question.	We appreciate that the case definitions are very different and that some are more inclusive than others and may reflect less severe cases or non-cases of ME/CFS as is fully outlined in the Key Question 1 response of the report. We also understand that comorbidities may also be present in patients with these symptoms. We decided a priori to include studies using any of the definitions to err on the side of being inclusive, and to highlight any differences between studies using different definitions that might present themselves.
Peer Reviewer #5	General	Key question 1 about the diagnosis ME/CFS overlaps with the charge of the IOM committee that is supposed to be evaluating current criteria for diagnosis. It is unfortunate that effort was spent on this question in both venues.	Thank you, your comment has been noted.
Peer Reviewer #5	General	The main policy decision that this report should make evident is needed is that additional funding is essential for ME/CFS research, to allow the examination of large cohorts with robust statistical significance, and to permit studies that replicate and extend initial results. Etiological studies are dismissed in the report because of the charge to the authors did not address them, but it is exactly such studies that are required before effective objective diagnosis and treatment will become possible.	The scope of this report was not to review etiology but rather to help inform on aspects of diagnosis and treatment of the syndrome ME/CFS. When biomarker studies reported on diagnostic accuracy or ways of correctly identifying patients with ME/CFS and those without, these studies were reported. We recognize that the biomarker studies may eventually provide insight into the etiology and potentially diagnosis of ME/CFS but its work is still in its infancy for diagnosing the syndrome of ME/CFS and has not been well studied in a way that reports diagnostic validity in patients with diagnostic uncertainty and thus did not meet our inclusion criteria.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	General	<p>My general response to the study is that the key questions are appropriate and explicitly stated. At present, the problem with a study of this kind is that the field of ME/CFS research including the study of sub-types is rapidly changing. Given that many in the field believe that there are indeed distinct sub-types it is difficult to rely on current diagnostic criteria e.g. Fukada or other definitions since patients with the disease can vary significantly. I believe that research into sub-types (and etiologies) will eventually lead to a better understanding of the disease which in turn may lead us to base diagnoses on real physiological data in addition to clinical manifestations. Also it is logical to assume that eventually effective treatments will be found to treat those of different sub-types. The Norwegian study on rituximab is an example of a treatment benefiting some patients with ME/CFS but not all. It may be that those who benefit from this type of treatment represent a certain sub-type.</p> <p>In terms of differentiating ME/CFS patients from those who have depression or RA or other conditions it is currently incumbent upon the physician to rule in or out other factors which may confound or clarify the diagnosis. My own physician was able to diagnose ME/CFS in short order after ruling out other possible causes of my symptoms. Other patients may not be so fortunate. But I do believe that in time there will be other more precise ways to determine if a patient has a variant of ME/CFS.</p>	Thank you for your comments. We appreciate you sharing your story with us, and hope that other clinicians are able to follow the example your physician has set.
TEP Reviewer #6	General	The report is well structured and organized. Clarity of the main points is compromised by the equivocal results of the studies reviewed. It does come across that better (funded?) ME/CFS research is needed if we are to move forward in the diagnosis and treatment of this devastating illness. But we already knew that.	Thank you.
TEP Reviewer #6	General	<p>generally well-researched and –written report that acknowledges most of the issues impacting ME/CFS research and treatment.</p> <p>There is nothing in the report that will assist in the diagnosis and treatment of ME/CFS, i.e., it is not clinically meaningful. This does at least appear to be acknowledged in the report.</p>	Thank you for our comment. The intent of the report was to inform the P2P about the evidence that is available, its limitation and applicability, and areas of focus for future research. It is outside of the scope of our work to recommend for or against a diagnosis or treatment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #6	General	There is little discussion of target population (symptomatic adults?) or audience (clinicians?). An issue that is insufficiently addressed is that of comorbidity. It is very common for “ME/CFS patients” to present with multiple pathologies which complicates both diagnosis and treatment. It is also the case that the clinician’s confronted by ME/CFS cover a broad range of disciplines and specialties, ranging from chiropractors to psychologists. This should at least be acknowledged in the report and the significance addressed, e.g., rheumatologists tend to focus primarily on musculoskeletal symptoms while an immunologist will focus on body chemistry. How might that impact a patient presenting with both ME/CFS and FMS?	Thank you for your comment. We have acknowledged the complications inherent in potential co-morbidities in key question one and indicated that future research should stratify patients based on characteristics including comorbidities. Our discussion. While the intended audience for the report is AHRQ and the NIH committee, we have attempted to revise the report to make it accessible to a broader audience, including clinicians and patients.
TEP Reviewer #6	General	For the most part key questions are appropriate but appear more general than explicit, e.g., Key question 1 mentions “patient subgroups”. There is much discussion among ME/CFS researchers about patient subgrouping and how to achieve this. It is difficult to be explicit about patient subgroups when there are no clear criteria for defining an ME/CFS subgroup.	Thank you. Your comment has been noted.
TEP Reviewer #6	General	The report is well structured and organized. Clarity of the main points is compromised by the equivocal results of the studies reviewed. It does come across that better (funded?) ME/CFS research is needed if we are to move forward in the diagnosis and treatment of this devastating illness. But we already knew that.	Thank you.
David Egan	General	I hope this fully informs you about ME. I would refer you to the web site www.me-ireland.com for a more comprehensive analysis of this illness, its dynamics, its diagnostic and its treatments, and the areas of research most likely to produce the best and most useful results. I would be happy to discuss this with you further, and help and assist you in any way I can to bring about effective biological based diagnostics and treatments for all ME patients.	Thank you for your comments and suggested resources. We have reviewed the website and appreciate the insight that it provided into this complex disease.

Commentator & Affiliation	Section	Comment	Response
Kartik A. Parekh	General	<p>AHRQ appears to have borrowed the combination term "ME/CFS" from NIH, which has quite recently begun using "ME/CFS" to mean the sum of any and all disease descriptions that include the terms CFS or ME, without any rationale for the inclusion of all such descriptions under a single clinical label, and lacking any formal or informal definition, let alone any kind of validation. The only truly formal use of the term "ME/CFS" was by the 2003 Canadian Consensus document [6], which sought to identify a legitimate clinical entity, as close as possible to previously described ME, from the excessively non-specific CFS constructs, while - perhaps unwisely - compromising on terminology. The term ME/CFS is also often used informally by clinicians, researchers, advocacy groups and patients for pragmatic purposes and to try to raise awareness of ME while acknowledging that ME is rarely given as a diagnosis in countries such as the United States, where most patients who better satisfy ME criteria have been diagnosed with CFS instead.</p> <p>By adopting the flawed premise that a clinical entity that unifies all ME and CFS constructs can actually be said to exist, the NIH-tasked AHRQ report became a tautological exercise, incapable of doing what was most necessary: critiquing two decades of research based on diagnostic criteria that have insufficient specificity and thus offer little hope of elucidating the pathophysiology of, or identifying treatments for, the various conditions that are captured by broad case definitions. Instead, by adopting the premise that ME/CFS is a single entity that may be sufficiently described by any of the extant case definitions of CFS, NIH and AHRQ are only compounding the diagnostic problems in ME and CFS research, while obscuring the more distinct clinical entity known as ME - the only one with a definition drawn specifically from the clinical study of epidemic cases.</p> <p>To quote Dr. A. Melvin Ramsay, author of that definition and a critic of the CFS construct:</p> <p>"...the failure to agree on firm diagnostic criteria has distorted the data base for epidemiological and other research, thus denying recognition of the unique epidemiological pattern of myalgic encephalomyelitis." [1]</p> <p>In the interests of scientific rigor and proper disease surveillance, NIH/HHS must not conflate established case definitions that have not been demonstrated to describe the same clinical entity. The primary inadequacy of the AHRQ report is the a priori nosological and semantic error of conceptually subsuming ME within the CFS diagnostic construct without sufficient validation.</p> <p>Absent a drastic revision of its current draft report that would reflect a real understanding of these fundamental nosological issues, I urge AHRQ to inform NIH that it cannot participate in P2P, nor publish an evidence review, on scientific and ethical grounds .</p>	<p>Thank you for your comments. We have elected to use the term ME/CFS at the outset of the report in order to not risk missing important and/or informative evidence that may be labeled under one term or another. By using these terms together throughout the report, we are not endorsing or refuting that these labels reflect the same disease state. We are hopeful that the evidence reported under research question 1 will help to shed light on this controversial topic for the P2P workshop. Additionally, one of the responsibilities of this report is to help identify limitations and applicability of the available research, as well as recommendations for future research.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #58	General	<p>Dear AHRQ:</p> <p>I have been severely disabled by myalgic encephalomyelitis (ME) since 1994. I am largely bedbound, unable to shower, and can't walk more than a few steps. I require a nursing home level of care. I am unable to leave my home except for medical appointments once or twice a year.</p> <p>Please answer the following questions:</p> <ul style="list-style-type: none"> • Why does your report never once mention the estimated 25% of ME patients who are homebound or bedbound, like me? Are you not aware of our existence, or did you deliberately choose to ignore us? If so, why? <p>The recommendations in your report are extremely harmful to people like me. As Dr. Ken Friedman said in a recent Medscape article, "If you're lying in bed and you can't move your head and you have to speak in whispers, graded exercise therapy is not going to help you, and were you to attempt it, it would most likely kill you."</p>	<p>We greatly appreciate your letter and questions. We had not discussed homebound patients--an oversight on our part--as they have not been able to participate in the trials. In learning more about homebound patients, we have added this to our discussion of limitations and applicability of the evidence and to the section on future research needs.</p>
Public Reviewer #58	General	<ul style="list-style-type: none"> • Why do you lump together eight case definitions? What proof do you have that they define the same clinical entity? Why do you ignore work that shows most of these definitions are unreliable and inaccurate? 	<p>We erred on the side of being more inclusive with the case definitions. As there is no agreed upon gold standard, we sought to evaluate all available evidence on these case definitions. We have expanded our discussion of the limitations, applicability and future research to highlight the need for subgroup analysis to determine how different populations may respond. We have reported on the available evidence of how these case definitions vary or are similar.</p>
Public Reviewer #58	General	<ul style="list-style-type: none"> • Why do you ignore critical cardiopulmonary and biomarker studies? 	<p>Reviewing the various theories surrounding etiology and the associated studies in biomarkers and cardiopulmonary studies was beyond the scope of this report. Any of these studies that reported on diagnostic testing were included.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #58	General	Why do you ignore all symptoms except fatigue? I have such bad muscle weakness that I often cannot brush my teeth. Yet you ignore muscle weakness and other symptoms. Why? Thank you. I support comments by Mary Dimmock, Claudia Goodell, Denise Lopez-Majano, and Jennifer Spotila.	During topic refinement, the questions were developed with the NIH working group and AHRQ. Given the breadth of symptoms that patients with ME/CFS experience, we could not have tackled all of these within the scope of this one report. In consultation with the technical expert panel, the working group and AHRQ, the key questions were set to focus on the syndrome of ME/CFS and the universally experienced symptom of fatigue. We will recommend areas of future research including a systematic review on PEM diagnosis and treatment which would be a topic unto itself.
Public Reviewer # 49	General	If the P2P had been asked to put stomach ulcers under a judge and jury model as you are doing for ME, you would have rejected the short course antibiotics intervention due to the length of the intervention and you would have definitely included papers pertaining to psychological- stress reduction- type A personality.	We performed a separate search for medications that would appropriately be given for less than 12 weeks and have included the trial of rituximab in our discussion as well as one trial of acyclovir.
Public Reviewer # 49	General	All the members on the panel will have a bias of some sort. Patients with ME encounter these characters on a regular basis. They are being told it's all in their heads, that they need CBT and GET. These physicians have learnt that from med school. This bias needs to be recognized. Most physicians have learnt to ignore patients with ME- for instance it is not a reportable disease. We do not usually or specifically die of ME. And while it can be fairly disabling, these physicians think this disease is not their department so said patients just drift away or disappear from that practice. It is safe to say that most physicians do not want such patients in their practice. The importance to recognize bias within the committee is crucial.	Thank your for your comment. The organization of the P2P meeting is beyond the scope of this report.
Public Reviewer # 49	General	The reviewers have not noticed that the PACE trial had major issues with changing their protocol halfway into the trial so more people could be declared 'recovered'. This trial was simply propaganda, and yet Lancet published it. The authors refuse to release the raw data to be examined by members of the public. The point is they had a mix of patients in their trials, all you need to be included was to have fatigue for 6 months. Patients with ME have much more than fatigue and as you know, fatigue is prevalent with all diseases including rheumatologic conditions, cancer, HIV and depression.	We agree that there are some limitations to the PACE trial and have expanded our discussion of this throughout the report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 49	General	You pointed on your report that all the definitions studied were about fatigue and that you were to study fatigue. I and many of my fellow patients want to tell you that the hallmark of our disease is not fatigue, but what is called post-exertional malaise, but even that name is insulting. I call it post-exertional relapse, or what Carruthers et al. call post-exertional neuro-immune exhaustion. This is what you need to focus on.	Thank you for your comment. In no way do we mean to be insulting or to diminish the experiences of patients with ME/CFS by the choice of wording we have used to describe your situation. We expanded the introduction to better relay the patient experience.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 49	General	<p>The P2P judge and jury model is using physicians who are not knowledgeable at all about ME, not knowledgeable about its history, the epidemics of the mid 1980's, the fact that CDC investigated the Incline Village epidemics and concluded that both patients and physicians were 'hysterical'. Therefore the panel starts with the bias of ignorance, and these panel members cannot be primed as of exactly what has happened in the last 30 years.</p> <p>Our ME experts have lived through the bias of medical journals not wanting to publish their papers. They have lived through applying for NIH grants, or any government grants and unless the research was of psychological nature, they could not get such grants nor could they get support from their peers.</p> <p>The P2P process has turned down or disregarded many many good papers relevant to the pathophysiology of ME and as a consequence, good science is being disregarded. The effect of this is that NIH will publish a paper discussing CBT and GET- when not one patient I know has recovered from their illness at all from CBT or GET. The harm it will do once more to the patient population is bigger than what P2P can realize because they are not cognizant of our history and political situation. All members of the panel needs to know that most prominent virus hunter professor Ian Lipkin (Columbia University) has been refused a NIH grant to research ME. Dr Lipkin received a 32 million \$ grant to research the micro biome, but not ME. What is it telling about the NIH grant review and its bias for ME? Judge and jury model does not work for us for grant review either. It was said somewhere that one of the reviewer for Dr Lipkin's grant felt that ME was psychological, therefore he didn't need to bother to search for infection.</p> <p>We, the millions of patients around the world have been left behind and taken advantage of by the psychiatric lobby. This is not a mental illness. And yet the P2P is leaving behind the evidence, the one that is not good enough for your reviewers, and yet has been the best that our experts could do with the very limited amount of funding they had, and the very limited help they could get. The danger of publishing a report such as the one you are preparing is enormous. You are damaging the patients, and their access to competent medical care. Some of us will commit suicide due to the lack of hope and lack of resources. Insurance companies will benefit from this report, using it to refuse claims.</p> <p>I am sorry I cannot provide accurate and professional response and supporting my evidence by literature. I am a sick person and my brain does not function well, especially when in the vertical position. It is hard to make sense of that for most physicians, however patients in my community will nod in approval. Dysautonomia does this to patients. And I bet that no paper pertaining to dysautonomia has been reviewed.</p>	<p>Thank you for your comment. The organization and process of the P2P workshop is beyond the scope of this review.</p> <p>In no way are we attempting to invalidate any patient's experience of their illness. Instead, it is truly our goal to review what evidence is available and to inform the P2P about limitations, applicability, and focus for future research.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #6	General	<p>It is unclear what is meant by "overlapping syndromes," but this seems to indicate a unique relationship between the stated diagnoses of ME/CFS, fibromyalgia, and depression (other diagnoses such as IBS are frequently cited in such a designation as well). This does not seem to be the case.</p> <p>Such diseases can of course be comorbid, and it's true that other illnesses should be watched for, as comorbid diagnoses will frequently have treatment strategies which could reduce morbidity, but we have no sound data to indicate the kind of unique relationship that seems to be implied with the usage of "overlapping syndromes."</p> <p>For example, fibromyalgia is known to occur as a common comorbid condition in lupus (22-25%), rheumatoid arthritis (25%), and Sjogren's (50%). [Bennet n.d.] Depression occurs in chronic diseases generally, possibly due in part to inflammation and other factors related to being ill [Voinov et al. 2013], and the rates of depression occurring in ME or CFS are similar to the rate of occurrence in other chronic illnesses, about 30-40% [Stein 2005], though this rate will vary based on how assessment is done, as some ways of assessment will classify symptoms of other illnesses as if due to depression (or anxiety, etc.) [Jerant 2014, Stein 2005, Blitshteyn 2009]. (As a side note, it seems that depression studies should also take care to stratify for or exclude ME/CFS, as some ME/CFS patients are diagnosed with depression without necessarily meeting any criteria for depression [e.g. Henderson 2014].)</p> <p>Besides these, some other examples of diagnoses noted to be comorbid with ME include Ehlers-Danlos syndrome, dysautonomia, Raynaud's, and asthma. [Underhill 2014, Raj and Rowe 2014].</p> <p>Of course, many of these diagnoses, such as POTS, IBS, and asthma, have various diverse possible causes, with more causes remaining unknown [Raj and Rowe 2014, Lee & Park 2014, Ray et al. 2014]. While it's possible that a single pathology such as mast cell activation disease [Molderings et al 2011] or autoimmune disease [liME 2014] might underlie several comorbid conditions in a given patient, it is unlikely that any single explanation would explain the entire set of ME/CFS + fibromyalgia + IBS (or whatever lumped conditions were being considered together), given the diversity of physiopathologies being studied to subgroup the various diagnoses.</p> <p>This sort of diversity of causes would be a logical working hypothesis to explain ME/CFS as well, and many leading researchers have taken an interest in subgrouping the illness [McGrath 2013, liME 2014].</p>	<p>We use overlapping conditions to refer to conditions that have similar symptoms and/or are often diagnosed together.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #59	General	<p>The AHRQ Draft Systematic Evidence Review is the foundation of the Pathway to Prevention (P2P) meeting on ME/CFS. If it is not done properly, the workshop and resulting recommendations will be wrong.</p> <p>One million Americans, including my daughter, and 17 million patients world-wide who suffer from ME depend upon a rigorous, thoughtful and scientifically valid P2P study. Good science is paramount. No short-cuts can be taken. Lives are at stake.</p> <p>Unfortunately, I believe the AHRQ Draft Systematic Evidence Review is seriously flawed. Bad or incomplete information leads to incorrect conclusions.</p> <p>I offer the following comments:</p> <p>1. The fundamental question that needs to be addressed is whether the eight (8) "ME/CFS" case definitions encompass the same disease, a spectrum of diseases, or separate, discrete conditions and diseases.</p> <p>It is my understanding that this fundamental question was posed in:</p> <p>A. the 2012 application for the Office of Disease Prevention to hold the P2P meeting;</p> <p>B. the 2013 contract between AHRQ and the Oregon Health & Science University for the systematic evidence review; and</p> <p>C. the P2P Working Group at its January 2014 meeting to refine the questions for the evidence review and workshop.</p> <p>It is essential that the AHRQ evidence review and the P2P agenda consider this fundamental question. The failure to tackle this cornerstone question in both the AHRQ evidence review and the P2P agenda puts the scientific validity of the entire P2P Workshop at risk.</p>	<p>Thank you for your comments. Our scope and Key Questions were developed by the Working Group and in consultation with our Technical Expert Panel.</p>
Public Reviewer #59	General	<p>The evidence review does not convey the seriousness of the disease. Post-exertional malaise (PEM) should be a focal point of discussion. When the FDA asked ME/CFS patients to describe their disease, they did not say "fatigue."</p> <p>Patients told FDA that post-exertional malaise (PEM) was the most significant symptom: "complete exhaustion, inability to get out of bed to eat, intense physical pain (including muscle soreness), incoherency, blacking out and memory loss, and flu-like symptoms."</p> <p>Multiple studies have demonstrated that patients with PEM have impairment in energy metabolism and lowered anaerobic threshold, and have shown that patients with depression, deconditioning and a number of other chronic illnesses do not have this kind of impairment.</p> <p>...Post-exertional malaise should also have been considered (as a symptom-related outcome). as drafted, the evidence review is incomplete ...</p>	<p>Thank you very much for your comment. We have added information to our introduction and discussion addressing the symptom of PEM and have added to the limitations of the studies regarding whether or not the case definitions use of PEM.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #59	General	Incorrectly, the report is heavily weighted towards psychological studies. Out of the 36 studies used to address Key Question 2, 14 concerned CBT. (page ES-8) It is my understanding that the SOLVE ME/CFS INITIATIVE wrote to NIH and said that the evidence review strategy will bias the results toward CBT/GET studies and miss very important biomarker studies. This proved to be true. My concern is that the Draft Systematic Evidence Review does not provide the depth of information the P2P panel should have in order to consider the issues and make informed recommendations.	We are limited by what is available in the literature and have reported all available studies that met inclusion criteria. We have expanded on the limitations and applicability of the intervention studies, particularly the CBT and GET studies.
Public Reviewer #59	General	Before the P2P panel proceeds with their analysis of the material and the workshop, it seems to me that several issues need to be addressed. A. Were the inclusion and exclusion standards too restrictive? B. Will the P2P panel have sufficient information to consider the issues presented and make informed recommendations? The importance of this question is underscored by the fact that the report does not arrive at any firm conclusions about how to define, diagnose or treat this illness. The report states: “The limitations in applicability as well as the limitations of evidence base make it difficult to draw firm conclusions with implications for clinical practice.” (Implications, page ES-29) “Most of the evidence available surrounding treatment is insufficient to draw conclusions.” (Implications, page ES-29) “Intervention studies were scarce and most were either fair or poor quality and measured outcomes using heterogeneous methods making it difficult to compare results across studies.” (Limitations, page vi) My concern is that the Draft Systematic Evidence Review does not provide the depth of information the P2P panel should have in order to consider the issues and make informed recommendations. Based on the information provided in the Draft Systematic Evidence Review, I do not believe the P2P panel members during their workshop will be able to reach scientifically valid conclusions. If the P2P panel cannot successfully complete their responsibilities, they should not proceed and the project should be stopped.	Thank you for your comment. We reported all available evidence that fulfilled the pre-defined inclusion criteria. Reporting on studies that do not meet these criteria would negate the science that makes these reports systematic and could lead to inaccurate interpretations. The P2P process will include additional presenters and will take into consideration additional information beyond the scope of the evidence review.
Public Reviewer #7	General	I wish to object most strongly to the AHRQ Evidence review ‘Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)’ which has been conducted in an extraordinarily unscientific manner. I have had about 40 years experience of close family members suffering from Myalgic Encephalomyelitis and so have experienced at first hand the damage and harm caused when different illnesses are confused. This type of confusion causes inconclusive research, misleading results and leads to patients being subjected to inappropriate management – causing irrevocable harm. I object very strongly to the underlying assumption that patients included by the	Thank you for your comment. We reported all available evidence that fulfilled the pre-defined inclusion criteria. We erred on the side of including more of the case definitions to present to the P2P all the information. We have expanded on the differences and variability in the case definitions used were applicable.

Commentator & Affiliation	Section	Comment	Response
		<p>criteria of eight very different CFS and ME definitions have the same illness or subgroups of the same illness. They just do not. Research relating to a particular group of patients identified by the criteria of specific definition can not safely be applied to patients selected according to the criteria of a completely different definition. Some of these eight definitions actually exclude patients with other definitions included in this report! For example the Oxford CFS criteria excludes patients with signs of neurological illness – which are necessary for a Myalgic Encephalomyelitis diagnosis.</p> <p>This absolutely basic flaw renders this review unscientific and utterly meaningless, by the most basic rules of logic and common sense. The deadly consequences of this type of confusion can be seen in the film 'Voices from the Shadows' https://vimeo.com/ondemand/22513/108797012</p> <p>Patients with mild to moderate ME become patients with severe ME and may die when they are given behavioural/psychological based treatments appropriate for a different set of patients with chronic fatigue, because the underlying neuro-immune inflammatory pathology of the illness is ignored.</p> <p>I wish to state my wholehearted agreement with the detailed 40 page submission by the parents, patients and advocates listed below –</p> <p>Mary Dimmock Claudia Goodell, M.S. Denise Lopez-Majano, Speak Up About ME Jennifer Spotila, J.D. Lori Chapo Kroger, R.N., PANDORA Org CEO and President Pat Fero, MEPD, President, Wisconsin ME & CFS Association, INC. Darlene Fentner Leonard Goodell, Jr. Alan Gurwitt, M.D. Wilhelmina D. Jenkins Joseph Landson, M.S. Margaret Lauritson-Lada Jadwiga Lopez-Majano Mike Munoz, PANDORA Org Board of Directors Matina Nicholson Charmian Proskauer Mary M. Schweitzer, Ph.D. Amy L. Squires, MPA Susan Thomas Erica Verrillo, Author</p>	

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Public Reviewer #60 Patient and Advocate	General	Over the past three decades, the disease known by the World Health Organization as “Myalgic Encephalomyelitis” has been misrepresented and distorted by those who lack a true understanding of the nature of the disease. The creation of overly broad definitions and a new name has only served to further obfuscate the situation. The draft AHRQ Evidence Review currently states “Multiple case definitions have been used to define ME/CFS and those that require the symptoms of post-exertional malaise and neurological and autonomic manifestations appear to represent a more severe subset of the broader ME/CFS population.” However, it is the decided opinion of ME/CFS experts, clinicians, patients and advocates that the symptoms of post-exertional malaise and neurological and autonomic manifestations represent ALL patients with the disease being measured. Patients who do not have these symptoms do NOT have the disease in question.	Thank you very much for your comment. We have added information to our introduction and discussion addressing the symptom of PEM and have added to the limitations of the studies regarding whether or not the case definitions use of PEM.
Public Reviewer #60 Patient and Advocate	General	It is my understanding that a vital Key Question was omitted as a workshop goal due to a lack of research: “Do the set of ME/CFS definitions encompass the same disease, a spectrum of diseases, or separate discrete conditions and diseases that do not belong together?” Respectfully, failure to separate this disease from other fatiguing illnesses (misidentified as “the broader ME/CFS population” in this draft) is a fatal flaw in this process. As you are likely aware, the Institute of Medicine is reviewing the issue of diagnostic criteria at this very moment. The National Institutes of Health and the AHRQ would be wise to delay a final report and the P2P workshop meeting until that study has been published. Unless and until that very basic question can be answered, the results of this workshop will be of little or no practical use.	The scope and key questions were developed in conjunction with the working group and our Technical Expert Panel. The P2P process is out of the scope of this review.
Elizabeth C. Potter Board of Directors, Massachusetts CFIDS/ME & FM Association	General	I am deeply saddened that after 20 or more years of constructive input from the ME/CFS community and the credentialed doctors who have participated in documenting and researching ME/CFS, the government organizations that are affiliated with the CFSAC team have virtually ignored all the information from the true experts. The true experts on ME/CFS are those of us who have been fighting for our lives, some of us have been in this Petri dish for nearly 30 years and those few doctors who recognize and believe our true condition. I have received the most help from doctors and practitioners who are willing to think holistically and/or were involved in research that veers off from the normal medical charter. We are a collection of educated professionals who got sick and are receiving very little constructive help from the medical community. Even worse, we are looked upon as faking it, perceived to have psychological imaginings, abused by the medical community at large and therefore our culture at large. There has been little sense of humanity toward our plight. We have kicked against the traces jeopardizing our own health to get attention and respect. Gratefully, there have been a few medical professionals who have seen the lack of humanity and have stepped forward while the medical community at large still	Thank you kindly for your letters in response to the AHRQ draft systematic evidence review on Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. And thank you for sharing your stories with our team. The devastating effects that this condition has had on your lives and those of other patients are better appreciated by allowing us the opportunity to see into your world for even a short time. We have additionally tried to improve our knowledge and understanding with aid of the Primer for Clinical Practitioners as well as multiple patient advocacy resources that we reviewed at the outset

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		<p>ignores their evidence. An international collaboration of medical experts, IACFSME, have presented the Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: A Primer for Clinical Practitioners which is widely accepted by the ME/CFS Community as accurate. The Canadian Criteria Consensus has also been acknowledged by our community as a valid representative document. We have stated numerous times the dangers of GET, which is known within our community as extremely detrimental and has been known to cause death in patients and yet it is still recommended in the medical community and by the CDC. CBT as well can have damaging effects. And yet, the medical community trudges forward chests held high that “they” “know” what is best, even though they are perplexed.</p> <p>Do any of you see the ignorance here? The lack of compassion? The inability to question the system that you work within? That maybe just maybe the medical establishment as a whole does not have all the answers. That maybe just maybe this is a CRACK in our medical system that needs to be explored. That maybe just maybe we need to have the vehicle to drive into this CRACK and explore without doctors having their livelihoods destroyed for being compassionate and for doing no harm. By applying therapies that are detrimental, you are doing harm; by doing nothing, you are doing harm; by following the only track that is guided by the AMA and pharmaceutical companies, you are doing harm; by ignoring the ME/CFS community and the seasoned scientists who have dedicated themselves through compassion to ME/CFS, you are doing harm. As phenomenal as medical science has become, the miracles that trained physicians can perform, it clearly does not apply in our specific case.</p> <p>I am in support of the response by Mary Dimmock, Claudia Goodell, Denise Lopez-Majano, Jennie Spotila and Erica Verillo that is posted on Occupy CFS; http://www.occupycfs.com/2014/10/15/evidence-review-comments-preview/</p>	<p>of this project. Although we cannot experience the condition as a patient would, we included patients and experts as members of our Technical Expert Panel, and strove to attend to their areas of concern and guidance as we prepared our report. Numerous comments surround the debilitating effects of post-exertional malaise or neuroimmune exhaustion that patients experience. We have highlighted that this area of research is essential however the purpose of this report was to focus on the syndrome of ME/CFS rather than the individual symptoms that a patient suffers. We looked for any evidence that differentiated subgroups of patients in how they responded to various interventions or how diagnostic methods might vary, but unfortunately found very little evidence that met our predefined criteria. We too would like to see improvement in the type and quality of studies that could better direct the care of patients with ME/CFS. It is our responsibility as independent investigators to strictly report on evidence that is currently available using a pre-defined and structured systematic method. One of the tasks requested was to draw attention to areas where research is lacking and to give our recommendations on where efforts should be placed in order to better guide funding, research, and clinical practice. One recommendation is that patients be stratified based on their baseline symptoms in order to better determine if some interventions are more effective or potentially more harmful for subgroups of the population. This has been difficult for</p>

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			<p>researchers to do in the past given that the studies have mostly been small and thus may not detect a difference even if a difference exists. Another recommendation is that studies perform sensitivity analyses to determine if differences in outcomes exist between patients who meet different case definitions of ME/CFS.</p>
Polly A. Gilreath	General	<p>I am writing to request the cancellation of the AHRQ's P2P Workshop on ME/CFS and its Draft Comparative Effectiveness Review because both are rife with flaws. I believe that the P2P Workshop results will negatively affect much needed ME research, public perception of ME, and treatment by physicians for years to come. I unequivocally object to the P2P for ME/CFS for these reasons:</p> <ul style="list-style-type: none"> • ME/CFS experts have already adopted the Canadian Case Definition for research. No new definition is needed. • The Workshop is examining the wrong illness. They are examining "medically unexplained fatigue," not Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. • NIH has not engaged or involved stakeholders in a substantive way. • The Workshop panel consists of non-ME/CFS experts. • HHS has made numerous contradictory statements about the purpose of the Workshop, so its goal is unclear. • The recent draft report, "Diagnosis and Treatment of ME/CFS," from AHRQ is inaccurate, self-contradictory, and reflects a poor understanding of ME/CFS research. AHRQ's Draft Report violates its own mission statement.* <p>The P2P workshop has not produced good science and sound recommendations. I hope you will give my concerns a fair hearing, and that you will cancel the P2P Workshop.</p>	<p>The request for cancelling the P2P workshop is beyond our authority. That said, we have received and listened to the concerns expressed by patients, advocacy groups, and researchers. We have adapted our report to also give voice to the concerns of patients. We have expanded our discussion of limitations and applicability and particularly focused on recommendations for future research.</p>
Sister Sandra Duma, OSF, MS Ed	General	<p>But let's get back to the above referenced article which can be found at http://www.mdpi.com/2079-7737/3/3/606/htm and is well worth your read. In the section describing ME, the authors state:</p> <p>We begin our discussion with a condition for which the hallmark-defining symptom is fatigue. Myalgic encephalomyelitis [6], often referred to as Chronic Fatigue Syndrome in the United States [7], is a devastating neuroimmune disease [8,9] displaying global disruption of the nervous, immune and endocrine systems [6]. Approximately 0.4%–1% of the adult US population has ME/CFS [10], although the percentage may be far higher considering the lack of widespread recognition of the disease in the general population and by the medical community. Symptoms include marked physical and cognitive fatigue, unrefreshing sleep, and a prolonged recovery period in response to even modest physical or mental activity. Muscle pain and fatigue are common symptoms, even</p>	<p>Thank you for your comment. The etiology of the disease was beyond the scope of this review.</p>

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		<p>at rest. Patients often develop fibromyalgia, a related neuroimmune disorder distinguished by chronic widespread pain and allodynia (a heightened and painful response to pressure) [11].</p> <p>Abnormalities are evident within the immune [12] and central nervous [13] systems that likely stem from defective oxidative and nitrosative pathways and a lower antioxidant status [14,15]. Mitochondrial function is depressed, with the severity of the disease correlating with lower oxidative phosphorylation, nucleotide transport, and ATP levels in blood neutrophils [16,17]. There is some evidence that compromised metabolic function extends to skeletal muscles [18] and other major organs [16]. In what may be a compensatory response, anaerobic metabolism is up-regulated via enhanced glycolysis [16,17]. The regulation may be structurally based in supramolecular complexes of glycolytic and glycogenolytic enzymes [19]. Cytoplasmic compartmentation and the formation of enzyme complexes probably boosts ATP production and, with further regulatory enhancement, may help alleviate the depressed aerobic metabolism evident in ME/CFS. However, any benefits of shifting from oxidative to glycolytic pathways may be offset, during periods of increased physical activity, by excess production of fatigue-producing metabolic by-products (phosphate and metabolic acids) [20].</p> <p>Metabolic defects may also be reflected in abnormalities in blood flow regulation and mitochondrial function, some of which may be linked to altered endothelial nitric oxide (NO) [21] and hydrogen sulfide (H₂S) [22] metabolism. NO relaxes the smooth muscles that surround arterioles and arteries, increasing the flow of blood when required. In ME/CFS patients, reduced NO production by endothelial cells [21] may increase the constriction of arterioles and arteries, whereas a postulated deregulation of H₂S [22] may lead to an inhibition of cytochrome-c oxidase and thus a reduction in mitochondrial production of ATP. A reduced blood flow or mitochondrial ATP production in critical organs, including the skeletal muscles, brain, and brain stem, could elicit a variety of somatosensory symptoms of ME/CFS, including a diminished ability to perform physical activity. [23]</p> <p>Skeletal muscle fatigue, the topic of interest here, likely contributes to post-exertional fatigue in ME/CFS. A small shift from fatigue-resistant, oxidative type I fibers towards oxidative, type II fibers occurs in some patients, with little or no attendant atrophy [24]. Nuclear magnetic resonance [25,26] and electromyography [27] reveal pathological features that are consistent with defective ion channel or receptor function [28,29,30]. Skeletal muscle mitochondrial function may also be blunted, as it is in blood neutrophils [16]. Oxidative stress [14,31] or autoantibodies [32] directed against mitochondrial proteins, plasma membrane proteins, or metabolic enzymes may play a role in the ME/CFS pathophysiology—all of which would lead to diminished physical</p>	

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		<p>activity. In addition, oxygen delivery to the patient's skeletal muscles is impaired [33], contributing to the metabolic insufficiency observed in the musculature of ME/CFS patients [34]</p> <p>In evaluating ME/CFS-related muscle fatigue, it is unclear to what extent aging and deconditioning contributes to the disease phenotype. Incorporation of these variables (particularly the former) into reported studies has generally been ignored. Research focusing on this issue is sparse, although one recent report shows diminished function of ventilatory muscles during exercise in ME/CFS patients that appears to be attributable to deconditioning [35].</p> <p>The above is certainly NOT medically unexplained fatigue, and as such ME should be removed from the CFS label by the very definition of CFS.</p> <p>A very important point is found at the end of the article: Figure 1 summarizes the challenge that researchers face in discerning the extent to which disease-related muscle phenotypes related to the primary disease versus muscle disuse—and the extent to which rehabilitation exercise therapy may correct or reverse the progressive development of muscle fatigue. The hypothetical time lines depict the primary effect of the disease itself (magenta hatched line) and the secondary effect of deconditioning (blue hatched line) on muscle physiological function, superimposed on the inevitable decline of function due to aging (green hatched line). The cumulative fatigue phenotype is the sum of all three. Exercise rehabilitation, which essentially counteracts the muscle disuse/deconditioning that accompanies many diseases, may be able to effectively remediate that specific component of the cumulative fatigue phenotype (difference between blue and red line). While this general approach undoubtedly cannot alleviate all of the symptomology of the condition, it may provide some symptomatic relief and allow patients to retain a higher level of functionality.</p> <p>An exception to the general utility of exercise rehabilitation is the one multi-system disease in which chronic fatigue is the hallmark symptom: ME/CFS. Even graded exercise therapy [99] is known to exacerbate ME/CFS by placing too much stress on the compromised systems, leading to a worsening of symptoms which may be injurious [100]. What is the recommended approach to easing muscle fatigue in ME/CFS? Proper nutrition combined with dietary supplements as needed, restorative sleep, and carefully pacing one's activities so as not to overtax the body [36].</p> <p>One last point: the story often repeated by many ME patients is that they were very active before coming down with ME when their lives abruptly changed. Therefore, deconditioning cannot be the cause of their ME.</p>	

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Public Reviewer # 39	General	<p>Still further, the following paragraph in the Executive Summary states: The term ME was first used in the 1930s after an outbreak of neuromyesthenia [sic] and CFS was first coined in the 1980s. [5-7] Attempts to describe the condition based on possible underlying etiologies led to additional terms including post viral fatigue syndrome and chronic fatigue immune dysfunction syndrome. [1,3,5,6] The most recent international consensus report advocates moving away from the term CFS in favor of ME to better reflect an underlying pathophysiology involving widespread inflammation and neuropathology, and to embrace the two terms as synonymous. [2] However, others believe that ME is a subset of CFS and represents a more severe form of the same disease. [4] Some feel that the lack of specificity surrounding the name, CFS, may delegitimize and negatively characterize the condition, and stigmatize patients. [8] For this review, ME and CFS will be used synonymously (ME/CFS) and will include the populations(s) studied under either of these terms, recognizing that issues regarding terminology are currently unresolved.</p> <p>The remaining references cited in this paragraph are: 5. Jason LA, Brown A, Clyne E, et al. Contrasting case definitions for chronic fatigue syndrome, myalgic encephalomyelitis/chronic fatigue syndrome and myalgic encephalomyelitis. <i>Eval Health Prof.</i> 2012;35(3): 280-304. PMID: 22158691. 6. Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: a working case definition. <i>Ann Intern Med.</i> 1988;108(3): 387-9. PMID: 2829679. syndrome. <i>Metab Brain Dis.</i> 2013;28(4): 523-40. PMID: 22718491. 7. Ramsay M. <i>Myalgic Encephalomyelitis and Postviral Fatigue States: The saga of Royal Free disease.</i> 1st ed. London: Gower Medical Publishing; 1986. 8. Jason LA, Taylor RR, Plioplys S, et al. Evaluating attributions for an illness based upon the name: chronic fatigue syndrome, myalgic encephalopathy and Florence Nightingale disease. <i>Am J Community Psychol.</i> 2002;30(1): 133-48. PMID: 11928774.</p> <p>The claim of the first sentence, "The term ME was first used in the 1930s after an outbreak of neuromyesthenia [sic] and CFS was first coined in the 1980s. [5-7]" is factually incorrect. The term ME was not used until the 1950s. The "outbreak of neuromyesthenia [sic]" in the 1930s presumably refers to an outbreak of polio-like illness, later considered to be ME, in Los Angeles in 1934 and well-documented by A. G. Gilliam in 1938 (Gilliam, 1938). Nowhere in the 1938 account is the term myalgic encephalomyelitis or ME used. To refer to the outbreak as "neuromyasthenia" is another anachronism, as the term was not used widely until the 1950s. Once again, if the Review authors had actually read the references they cite, it is unlikely they would make such obvious errors. Such academic sloppiness would not be acceptable in a PhD dissertation, nor should it be acceptable in an important government report.</p>	This has been clarified

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Public Reviewer # 39	General	Nothing in Reference 4 justifies the statement in the Draft Review, "However, others believe that ME is a subset of CFS and represents a more severe form of the same disease. [4]" The statement in Reference 4, "Findings indicated that the ME-ICC identified a subset of patients with more functional impairments and physical, mental, and cognitive problems than the larger group of patients who met the Fukuda CFS criteria." (Jason, 2013) refers to patients meeting ME criteria as a subset of the specific group of patients, the set, recruited for the study meeting the broader 1994 case definition of CFS. Nowhere in Reference 4 do the authors speculate or state their belief that "ME is a subset of CFS and represents a more severe form of the same disease." Using Reference 4 to support the Review authors' contention that others believe ME to be a subset of the "same disease" CFS is unwarranted.	Thank you for your interpretation. We have reviewed the reference. No change.
Public Reviewer # 39	General	<p>More troubling and further grounds to question the appropriateness of selecting the Review authors as a source of allegedly authoritative, objective knowledge for an even more unknowledgeable P2P panel is the following statement in the same paragraph:</p> <p>The most recent international consensus report advocates moving away from the term CFS in favor of ME to better reflect an underlying pathophysiology involving widespread inflammation and neuropathology, and to embrace the two terms as synonymous. [2]</p> <p>It is difficult to see this statement as other than a deliberate misrepresentation of the ME ICC designed to mislead the naive P2P panel. It is a shocking breach of intellectual integrity and surely grounds to disqualify the Review authors from completion of their contract. The ME ICC clearly recommend sole use of the term "myalgic encephalomyelitis" for patients meeting the ICC and removal of those patients from the broader, overly inclusive diagnostic category of CFS. Did the Review authors really expect no one would notice this egregious misrepresentation? What possible statement in the ICC would remotely suggest that the ICC authors would "embrace the two terms [ME and CFS] as synonymous"? The ICC authors do state that ME is "referred to in the literature as chronic fatigue syndrome (CFS)" however they clearly take exception to the confounding or combination of the two terms:</p> <p>The label 'chronic fatigue syndrome' (CFS) has persisted for many years because of the lack of knowledge of the aetiological agents and the disease process. In view of more recent research and clinical experience that strongly point to widespread inflammation and multisystemic neuropathology, it is more appropriate and correct to use the term 'myalgic encephalomyelitis' (ME) because it indicates an underlying pathophysiology. It is also consistent with the neurological classification of ME in the World Health Organization's International Classification of Diseases (ICD G93.3). (Carruthers, 2011, page 327)</p>	Thank you for your comment. In no way are we trying to mislead any reader of the report but rather want to emphasize that throughout the report, we have used the two terms, ME and CFS, together, while recognizing that differences do exist. We have attempted to highlight those differences in Key Question 1.

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Public Reviewer # 39	General	<p>The ICC recommend that patients meeting the ICC be removed from the broader, overly inclusive CFS category in this statement: "Individuals meeting the International Consensus Criteria have myalgic encephalomyelitis and should be removed from the Reeves empirical criteria and the National Institute for Clinical Excellence (NICE) criteria for chronic fatigue syndrome." (Carruthers, 2011, page 334)</p> <p>The authors of the ICC further elaborate this principle in the 2012 International Consensus Primer (ICP) (Carruthers, 2012):</p> <p>Remove patients who satisfy the ICC from the broader category of CFS. The purpose of diagnosis is to provide clarity. The criterial symptoms, such as the distinctive abnormal responses to exertion can differentiate ME patients from those who are depressed or have other fatiguing conditions. Not only is it common sense to extricate ME patients from the assortment of conditions assembled under the CFS umbrella, it is compliant with the WHO classification rule that a disease cannot be classified under more than one rubric. (Carruthers, 2012, page ii)</p> <p>The IC Primer also objects to labeling ME patients who meet the ICC with confusing hybrid terms containing the term CFS:</p> <p>Misperceptions have arisen because the name 'CFS' and its hybrids ME/CFS, CFS/ME and CFS/CF have been used for widely diverse conditions. Patient sets can include those who are seriously ill with ME, many bedridden and unable to care for themselves, to those who have general fatigue or, under the Reeves criteria, patients are not required to have any physical symptoms. There is a poignant need to untangle the web of confusion caused by mixing diverse and often overly inclusive patient populations in one heterogeneous, multi-rubric pot called 'chronic fatigue syndrome'. We believe this is the foremost cause of diluted and inconsistent research findings, which hinders progress, fosters scepticism, and wastes limited research monies. (Carruthers, 2012, page ii)</p>	<p>Thank you for your comment. In no way are we trying to mislead any reader of the report but rather want to emphasize that throughout the report, we have used the two terms, ME and CFS, as one term, while recognizing that differences do exist. We have attempted to highlight those differences in Key Question 1.</p>

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Public Reviewer # 39	General	This unsound methodology renders the entire Review valueless for comparing the merits of research studies done on disparate groups of subjects selected using various, widely differing case definitions. There is no rational way to determine the specific patient groups to which research results apply. To claim the ICC authors "embrace" the two terms ME and CFS as "synonymous" is an outrageous breach of basic standards of professional writing by the Review authors. It is surely sufficient to indicate the remainder of the Draft Comparative Effectiveness Review is unreliable and untrustworthy. Just as a PhD candidate would be removed from a degree program for displaying such intellectual and ethical standards, the authors of this Draft Review have shown themselves to be unworthy of completing their work. The Agency for Healthcare Research and Quality should cancel their contract immediately to prevent the unreliable and ethically compromised work of these authors from being further legitimized by the US government.	We used standard systematic review methodology. We have highlighted the differences in the case definitions used in the studies and where applicable have further noted the limitations of the studies in the discussion.
Public Reviewer # 56	General	My comments on the Review concern mainly the role of exercise studies in 'ME/CFS' with special reference to the PACE trial which has been considered 'good quality' in your Review and has been influential. It is disappointing that the CBT/GET studies emerge as dominant sources of evidence on the role of exercise in 'ME/CFS' in this Review. The authors conclude that CBT and GET 'show some benefit' but have only 'moderate confidence' in these benefits while noting that 'GET was associated with a higher number of reported harms and withdrawal rates in several trials'. ¹ Indicators of these harms named in the Review are patient drop-outs, follow-up failures and poor physical performance the exercise studies . ¹ These are found in the 6 Minute Walking Test (6MWT) in PACE (See below) ² a step test ³ and a treadmill test. ⁴	We have added information on the additional harms from the PACE trial and have included additional publications from this trial. We have elaborated on the limitations of the PACE trial.
Public Reviewer # 56	General	The Review has not highlighted the fact that the conclusions of the CBT/GET studies mostly rely on outcome measures consisting of self-reported tick-a-box tests measuring a variety of dimensions. When these measures show improvement, however modest, the authors declare them a success without regard to the frequent failure of the treatments to translate into significant improvement in objectively measured physical performance, the result sought by patients. They persist with the treatment, without questioning their assumptions about the condition they purport to treat and ignore the biomedical evidence underlying the condition.	Thank you for your comment. We have expanded our discussion and future research sections to highlight the need for objective measures surrounding specific symptoms of ME/CFS, specifically those that are most debilitating for patients, including PEM.

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Public Reviewer # 56	General	These unfavourable results should send the reviewers in search of possible explanations in the literature. Instead, we find that biomedical studies addressing these issues have been excluded because they failed to meet various formal inclusion criteria.	The purpose of this report was to review the diagnosis and treatment of the syndrome of ME/CFS. Where applicable, we have included biomedical studies. It was not the purpose of this report to review the underlying etiology or come to any conclusions about a biomedical cause.
Public Reviewer # 56	General	Examples of exclusion are the CPET studies which identify abnormalities in impaired heart rates and lower oxygen consumption on the second day of exercise, thereby providing significant insights into the onset and mechanisms of PEM. 5,6,7,8 It is incorrect for the reviewers to say that 'experts have identified critical features of the condition including PEM, however current methods of testing, comparing, and monitoring this symptom are lacking'. ¹ Even if these studies do not meet technical inclusion criteria, their findings begin to explain the poor and inconsistent results of exercise studies and to untangle the problem of heterogeneity by contributing to the identification of sub-groups, thereby addressing the aims of Key Questions 2a. b. and c.	Thank you for your comment. We have reworded this section - we did not specifically consider the outcome of PEM. That said, included studies did not report on this outcome. We have expanded our discussion and future research sections to highlight the need for objective measures surrounding specific symptoms of ME/CFS, specifically those that are most debilitating for patients, including PEM.
Public Reviewer # 56	General	If the aim of P2P and the Review is to advance thinking about 'ME/CFS', then it is sadly remiss in omitting evidence gleaned from biomedical studies. This approach can only lead to an imbalanced report and stifle future thinking and research into the condition. Surely, the AHRQ has an ethical duty not to risk the perpetuation of harms for patients by withholding important information from P2P.	The evidence report is only one of a multitude of contributors to the P2P Working Group to help inform decisions.
Public Reviewer # 56	General	The Review does not mention the dearth of studies of more severely affected patients, some of whom are house or bedbound. They cannot do exercise, let alone participate in exercise studies and so the conclusions of the Review, weak as they are, are skewed. For an insight into the effects of severe ME, I recommend the video 'Voices from the Shadows'. ¹⁹ As noted in the Review, more severe cases are more likely to be identified by the International Consensus Criteria (ICC) ⁹ , not surprisingly, as these criteria are based on clinical examinations of thousands of patients by expert doctors. This is in contrast to the Oxford Criteria which rely mainly on fatigue.	Thank you for directing us to the "Voices from the Shadows," a videotape we previously reviewed and also found very informative. We have expanded the applicability section of our report to address the fact that the most severely affected patients would have been excluded from most trials, given that they would have been required to attend sessions. One of the future research needs may be to include funding for directly observed home care interventions, including home exercise.

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Public Reviewer # 56	General	Your Review states, '(We) recognize that some of the earlier criteria, in particular the Oxford (Sharpe, 1991) criteria, could include patients with 6 months of unexplained fatigue and no other features of ME/CFS. This has the potential of inappropriately including patients that would not otherwise be diagnosed with ME/CFS and may provide misleading results.' and 'Although most of the pharmacological trials were targeting an underlying pathophysiological dysfunction, most of the other interventions were targeting associated symptoms of the disease. ¹ Unfortunately, the authors only hint at this significant problem without exploring its implications for treating ME and CFS as synonymous terms. They also disregard the fact that the CBT/GET studies generally use the Oxford Criteria which refers to CFS, not ME.	Thank you for your comment. We have expanded our discussion on how the case definitions may have influenced the results and have highlighted the case definitions more extensively throughout the report.
Public Reviewer # 56	General	The PACE authors recognise the difference in the conditions in noting that 'The PACE findings can be generalised to patients who also meet alternative diagnostic criteria for chronic fatigue syndrome and myalgic encephalomyelitis but only if fatigue is their main symptom. ² It is unclear, however, if this caution is intended for patients with PEM. The results of PACE also cast doubt on this generalizability to ME.	We have expanded our presentation of the PACE data including two additional publications. They did perform a sensitivity analysis with those patients meeting the CDC CFS (Reeves, 2003) and London ME (Sharpe, 1996) criteria and found similar results.
Public Reviewer # 56	General	Adherence to criteria in the studies is of importance but not guaranteed: the PACE trial intended to use the Oxford Criteria ¹⁰ which does not include PEM. Yet, reportedly, 51% of subjects with PEM found their way into the trial, meeting the London criteria. ² This loss of control of the sample characteristics has not been discussed by the PACE authors, who had an opportunity here to compare the PEM sub-group's performance in the 6MWT with the performance of those without PEM. No mention of such an analysis is apparent in the reports.	Thank you for this insight. This is a good example of how the case definitions overlap.
Public Reviewer # 56	General	As your Review point out, the CBT/GET trials purport to treat a different condition from biomedical studies which use criteria other than the Oxford. The PACE trial, in relation to GET, uses the 'the deconditioning and exercise intolerance' theories which 'assume that the syndrome is perpetuated by reversible physiological changes of deconditioning and avoidance of activity' with 'increased perception of effort, leading to further inactivity. ² According to a further elaboration by the authors, CFS is 'defined by a patient's reported symptoms', rather than objectively measured criteria. ¹¹ In the CBT/GET studies such as PACE these are not 'associated symptoms of the disease', but the 'disease', which also involves patient attitudes thought to perpetuate the condition. The authors have not established the existence of such a condition, rather, this theory appears to be a favoured explanation, applied to a poorly diagnosed condition. While exercise intolerance is certainly part of ME, the reason for it is not 'avoidance of activity' – rather, avoidance of activity occurs because of intolerance of exercise. In a self-contradiction, 'exercise intolerance' does not form part of the Oxford Criteria, which is supposedly used here.	Thank you for your comment. We also have reviewed comments by the PACE investigators and suggest that your comments would likely be of interest to those investigators as well. It is beyond the scope of this review and our expertise to determine the mechanism of action that has driven the changes noted in the study.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 56	General	<p>The PACE reports make no mention of the reversal expected by the theory, which apparently did not occur. Instead, in a follow-up report , there is a switch to the term 'recovery'.¹² This paper illustrates how a definition of recovery has been constructed without regard to objective physical performance, as measured by the 6MWT. The definition itself has other problems.</p> <p>This paper reports that 32 out of 144, or 22% of subjects 'recovered' after GET treatment. The composite criteria used for recovery includes the SF-36 score. In the course of the trial the threshold SF-36 score for recovery was changed from 85 to 60, lower than the score of 65 required at some points upon entry into PACE. (The original entry score was also changed from 60 to 65 mid-trial.) This made it possible to reach a 'recovered' score which was the same as or lower than the entry score.^{2,12} How many subjects relied on this lower score to be classified as 'recovered'? How many reached the original post-treatment threshold score of 85? These figures are not reported.</p>	<p>Thank you - we added the 6-minute walking test as an outcome of function from the PACE trial and have added the outcome of recovery to the report. We appreciate that meaningful "recovery" is not yet defined for ME/CFS and have added this to the discussion of future research needs in our report. We have also expanded on the limitations of the PACE trial.</p>
Public Reviewer # 56	General	<p>Your Review also fails to mention the results of the 6 Minute Walking Test in PACE, the only objective test included in that trial². In a sample of patients whose average age was 38 years, the best distance walked in six minutes reached a mean of 379 metres in the GET condition, a gain of 67 metres after 52 weeks of treatment. This is only 35 metres more than the specialist medical care (SMC)-only group. The CBT group showed no improvement compared with the SMC group². In other studies the 379 metres was exceeded by older patients with chronic heart failure, who managed 402 metres¹³ and by patients listed for lung transplantation.¹⁴ The PACE authors also refer to 'concerns about patients with CFS coping with physical exertion', the reason they were given no encouragement to walk faster in the final 6MWT¹¹, confirming the unrecovered state of the patients at the conclusion of PACE. Twenty-eight percent of patients for this test were lost to follow-up, more than for the self-report measures. ¹¹ On the basis of these results the rejection of the PACE deconditioning hypothesis is indicated. The physiology-based CPET studies also contradict the deconditioning hypothesis. There is no discussion of this issue in the PACE reports.</p>	<p>Thank you - we have added the 6 minute walking test as a measure of function but do recognize that although statistically significant, the clinical (functional) significance of this outcome is uncertain. It is the purpose of our report to present the evidence (data) but not to expand on individual hypotheses regarding the underlying cause/etiology.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 56	General	The authors have refused to provide data which might validate the self-reports with the 6MWT results. How many patients who 'recovered' with a significantly improved SF-36 score also walked the distance expected from a recovered person? The absence of this data has been queried in correspondence published by Psychological Medicine ,15,16,17 eliciting no satisfactory response from the authors who, instead, minimized the value of objective data for this condition 11. A Freedom of Information Request for this data was refused for different reasons at different times ²⁰ . Thus, evidence which should have been published, on which therapeutic policies are based, is being withheld. However, the authors have acknowledged that 'objective measures of physical activity have been found previously to correlate poorly with self-reported out-comes'. ¹²	We also have reviewed the responses of the PACE authors in preparing the review.
Public Reviewer # 56	General	The PACE trial fails to demonstrate useful effects on physical performance for 'ME/CFS' patients. Any conclusion of effectiveness of GET appear to rely on weak and ambiguous data and then only for a small number of patients, or data which has not yet been released. For further details of my critique of the PACE trial I draw your attention to my paper. 18	Thank you - this has been reviewed.
Public Reviewer # 56	General	The Review occupies itself with the results of a plethora of measures used in CBT and GET studies which sidestep the central issue of meaningful physical improvement from these treatments. It makes no contribution toward finding reasons for these failures, ignoring biophysical explanations which have been offered. GET is being imposed even as it is based on misconceptions about the physiological underpinnings of ME. The P2P must not be instrumental in continuing this situation. The review and P2P need to acknowledge the failure of the CBT/GET model and its assumptions and to take seriously the harms recognized in the Review and further harms. They need to recognize and facilitate research into the discovery of the underlying biomedical factors. Accepting the ICC would be a good start.	We have expanded on the CBT and GET results, including discussion of meaningful and clinical change.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	As a minor comment, the organization of this report is terrible. I have spent more than 20 hours going through this document; much of it wasted time because of the organization. No consistency in the headings of sections, the terribly planned and produced tables that are full of redundancies, the interposition of excluded and included references, the lack of availability of most of the articles cited, and many other problems need correction as well.	Thank you for your comment. The standard format for systematic reviews as set forth in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews was followed for the organization of this report. We have made some significant changes from the draft to the final report to improve the readability of the report, including making the executive summary more succinct, reformatting the structure of Key Question 1, rewording the key points for greater consistency between sections, and improving the readability of tables. The availability of references is outside our control.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	<p>The Objectives of this manuscript were stated as : “This review summarizes current research on the clinical diagnosis of ME/CFS and the efficacy and harms of multiple medical and nonmedical interventions to treat ME/CFS in adults.” This review completely fails to summarize current research in these areas. Less than 1% of the recent literature was even included in this review. The included literature in no way represents the best of the recent literature.</p> <p>It isn't clear where and why things went so wrong with this review. It is possible that the some of the problem was simply the constraints placed on these types of reviews by AHRQ are to blame, (although for Diagnostics there are no printed Methods in the Guide). There is a note that justifies the low inclusion rate on page 78 “...the general consistency of our findings with other systematic reviews, provides some assurance that our review was not biased by our selection criteria”. If this is indeed the case, AHRQ may need to thoroughly investigate and improve their methods for doing systematic reviews.</p> <p>Anyone familiar with the ME/CFS literature would be shocked with the studies chosen for inclusion, and even more shocked by the studies excluded. For those not familiar with the literature, the included studies would lead to the conclusion that ME/CFS publications are all in obscure, very low impact , not freely obtainable journals. Even the included studies from the few top researchers in the field that “made the criteria for inclusion” are not the best efforts from these groups. This lack of quality is simply not the truth. This indicates that something went seriously wrong in the process here.</p> <p>My recommendation is to start over.</p>	<p>It is our responsibility as independent investigators to strictly report on evidence that is currently available using a pre-defined and structured systematic method.</p> <p>(www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayProduct&productID=558#pdf) This includes avoidance of literature that does not have a pre-defined comparator group as well as opinion pieces and reviews that are not systematically performed--these publications have a great risk of incorrectly influencing the interpretation due to bias. The mandate for this review was to review the science around the diagnosis and treatment of the syndrome of ME/CFS; thus any literature pertaining to the underlying etiology (cause) or to diagnosing/treating one associated symptom such as PEM, was outside the scope of this report. However, one of the tasks requested was to draw attention to areas where research is lacking and to give our recommendations on where efforts should be placed in order to better guide funding, research, and clinical practice. We hear your concerns and have expanded our future research section to reflect the interests of patients and patient advocacy groups.</p>

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	<p>1. Better define the Key questions, using more input from true experts in this area. 2. design a different algorithm for searches. 3. Do a better job of evaluating which articles to include and exclude, 4. Include an oversight group of ME/CFS patient groups and researchers that are consulted at all steps in the process to prevent the “committee syndrome” which always results in mediocre conclusions. In terms of utility, while also suffering from the “committee syndrome”, “Myalgic encephalomyelitis: International Consensus Criteria” is a far more useful publication for physicians and patients, and groups attempting to determine existing diagnostics and treatments for ME/CFS. Consulting this as a first step could be useful.</p>	<p>Thank you - we have reviewed the International Consensus Criteria document and have found this very helpful in understanding ME/CFS. The process of determining the key questions and methodology surrounding inclusion, exclusion, and search criteria was multifaceted and included the Working Group, oversight from AHRQ, and technical experts throughout the process. A systematic review involves set methodology and some of the questions that arose, although valid, are not consistent with the review process. The P2P Working Group will be hearing from other experts during the workshop to help inform decisions on those topics outside the scope of this report.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 50	General	<p>Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is an often disabling condition with devastating effects on patients' lives and on the national economy. As noted by the Draft AHRQ Report on Diagnosis and Treatment of ME/CFS (Draft Report), more than one million Americans suffer from ME/CFS [ES-1], and, once afflicted, "most adult patients never [return] to work" [ES-2]. Not surprisingly, the economic impact of this disease is "considerable" [ES-2]. Despite the scope of this problem, there are "no medications for the treatment of ME/CFS approved by the U.S. Food and Drug Administration," "no accepted diagnostic tests or treatments," and not even any understanding of a "clearly identifiable etiology and disease process" [all at ES-2]. In recent years, ME/CFS research has uncovered promising findings in areas as diverse as autoimmunity, neuroinflammation, mitochondrial dysfunction, cytokine levels, viral activation, and endocrine disruption. However, annual federal funding for ME/CFS research is approximately \$5 million dollars – much lower than the norm for any other condition with a similar scope and health impact. Due to this severe and continuing shortage of funding, most ME/CFS studies are very small and designed with an eye to conserving scarce funds. The overall funding situation is so dire, the patient community has even resorted to crowd-funding to keep the pace of research moving forward.</p> <p>With this background, any developments that might aid ME/CFS research are welcome. Although the patient community is sometimes viewed as hostile to government efforts related to ME/CFS, in fact we would be thrilled for any assistance in support of the many areas of critical research that are still lacking. Everyone would be pleased if this AHRQ report process really fulfilled its intention to enhance the state of ME/CFS research by summarizing in one place all the "current research on the clinical diagnosis of ME/CFS and the efficacy and harms of multiple medical and nonmedical interventions to treat ME/CFS in adults" [v]. Unfortunately, by employing questionable methods to select the evidence considered, then relying on that faulty evidence to report misleading results and conclusions, this Draft Report misstates the field it seeks to clarify. Moreover, because the AHRQ also expects that its final report "may be used ... as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies" [ii], this flawed Draft Report runs a risk of misleading the health care system at large. This misleading information could bring real harm to the million-plus ME/CFS patients in their search for medical care and for the insurance coverage to pay for it.</p> <p>Like many other patients, advocates, and researchers from the ME/CFS community, I recommend that any final report must, at a minimum, (1) remove any studies relying on the scientifically questionable Oxford definition of ME/CFS, (2) remove references to the widely discredited PACE trials, and (3) rewrite the two misleading statements of Conclusions.</p>	<p>Thank you for your comments. We have edited the conclusions section to reflect that ME has more severe symptomatology when compared with CFS definitions.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 50	General	<p>In light of a “key question” related to the potential harms of a ME/CFS diagnosis, the Draft Report states several times that a diagnosis of ME/CFS carries proven harms. The discussion correctly acknowledges that these harms can stem from prejudice in the medical community, a lack of understanding about ME/CFS, and the chronic and disabling nature of the disease [ES-11, ES-27]. As a patient, I can confirm that, quite simply, it’s stressful to lose your vitality to a severely disabling disease that your doctors can’t even explain, much less fix. It’s worse still when many doctors stigmatize the disease and the public at large doesn’t understand it. But I genuinely don’t know what to make of the statement in the Results that a “diagnosis of ME/CFS is associated with broad psychosocial consequences” [v] and in the Conclusions that “GET appears to be associated with harms in some patients whereas the negative effects of being given a diagnosis of ME/CFS appear to be more universal” [vi, ES-80]. I don’t understand the logical connections in those sentences well enough even to suggest a correction. The negative effects of a ME/CFS diagnosis come from the lack of hope for treatment and improvement – directly from the lack of good research as reflected in this Draft Report – not from some quality inherent in the diagnosis itself.</p>	<p>Thank you for your comment and for sharing your experience with us. We have expanded on our discussion of the benefits and harms of being diagnosed.</p>
Public Reviewer # 51	General	<p>To begin, I want to state my overall opposition to the Pathways to Prevention Workshop as a strategy to address research gaps in ME/CFS. My objection is based on the following:</p> <ol style="list-style-type: none"> 1. The use of non experts to review and interpret the research. ME/CFS is a complex disease that is poorly understood by general practitioners and researchers. There are a handful of experts who have been involved in clinical practice and/or research who would be much better at providing interpretation and recommendations for future research. The deliberate use of “non experts” via a “jury model” coupled with the void of large scale robust research, due to significant underfunding, seems unfair at best and at worst appears to be a deliberate attempt by HHS/NIH to squelch further research into identification of biological causes and treatment. 2. The lack of a standardized definition used in both clinical diagnosis and research thus far that does not allow for separation of people with the main symptoms of post-exertional exacerbation of symptoms, neurocognitive, autonomic and immune dysfunction etc. from people who are just tired, or depressed, like the Oxford criteria used by the PACE trial. It also makes it very difficult to compare studies against one another to aid in answering the P2P questions as the populations studied cannot be assumed to be the same and therefore conclusions should be suspect. For case definition, I recommend that the P2P support the 50 experts and 66 advocates that have asked the former HHS secretary to adopt the Canadian Consensus Criteria. 3. There simply was no need for HHS/NIH to commission the P2P project, 	<p>The process of the P2P is out of the scope of this review. We included experts throughout the process of the review and in developing the scope and key questions.</p>

Commentator & Affiliation	Section	Comment	Response
		<p>instead, they could have just honored requests made throughout the 10+ year history of the Chronic Fatigue Syndrome Advisory Committee (CFSAC). A congressional initiative currently underway called the 21stCentury Cures Initiative, has produced a common theme arising from roundtable meetings around the country. The theme is about involving patients in setting the research agenda for NIH, academia, industry and consortia. With its' patient/advocate members, clinical experts and government official representation, CFSAC could be a prime example for how to involve key stakeholders in developing a research agenda. But instead of listening to CFSAC, HHS/NIH commissioned the P2P project which seems to be working in direct opposition of patient/expert involvement. Like the saying, "if you are not at the table you are probably on the menu", it sure feels like ME/CFS patients are being served up on the chopping block by the P2P process.</p> <p>4. The P2P questions are wrong and seem to have been changed from the original to something too narrow in scope. If the AHRQ report is any indication of the direction to be taken by the P2P it appears to be deliberately biased in favor of behavioral interventions while eliminating non-behavioral based etiologic/treatment research and disregarding the major issue of multiple case definitions. As a result, the only possible outcome from the P2P process is likely to be a bad one for ME/CFS patients resulting in possible harm due to mistreatment and/or financial hardship because of insurance and disability benefit denials and continued prejudice and stereotyping by health providers, the media and the general public.</p>	
Public Reviewer # 51	General	<p>AHRQ report: Pg. ii 3rd paragraph Comments: This paragraph should be stricken. The purpose of this report is to support the Pathways to Prevention Workshop for "Advancing the research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome". This report should not be used for "clinical guidelines" or as a "basis for reimbursement or coverage policies".</p>	We have revised this section.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 51	General	<p>In summary, information and conclusions outlined in the draft AHRQ Report seem to provide little help for the P2P workshop to accomplish its' goal of "Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome". By contrast it looks like it is setting the stage to do the opposite, as it is more than likely to result in promotion of psychological and behavioral interventions that ME/CFS patients say do not help to reduce symptoms and disability, and for some, have actually caused progression of the illness. The notation in the Report that it may be used for clinical guidelines and coverage decisions is also particularly concerning. It appears that HHS is looking to provide fuel for the insurance industry, Medicare/Medicaid and Social Security to deny coverage for medical and disability benefits for ME/CFS patients, similar to what has happened in the United Kingdom.</p> <p>Missing from the report is data on NIH funding for ME/CFS which is critical to the P2P discussion. Affecting an estimated 1 million plus people in the US, ME/CFS receives around 5 million dollars annually for research or roughly \$1.56 per affected life per year versus HIV affecting the same number of people, which receives closer to \$25,000 per patient per year. Yet due to treatments available to HIV patients, patient disability is actually higher in ME/CFS and is comparable to end stage AIDS. Several highly profiled and respected researchers in the U.S. from institutions like Columbia and Stanford have been denied NIH funding for ME/CFS, yet they receive large grants for other projects, why is that?</p>	<p>The purpose of the report remains to present evidence from existing research on diagnosis and treatment of ME/CFS and to identify future research needs. The preface to the report has been revised.</p>
Public Reviewer # 51	General	<p>Also missing from the report is how the disease affects children and adolescents as well as comprehensive morbidity and mortality information on the disease. There is no information about the degree of disability and progressive nature of the disease that has low (<10%) reported "true" recovery rates, not those alleged by PACE with their manipulated data. Studies on the severely disabled, homebound/bedbound population, estimated to be up to 25% of people in the U.S. with ME/CFS, are missing from the research which is a huge void that needs to be addressed. Early mortality is another important issue that is not addressed in the Report. The average age of death is reportedly lower than the general population due to higher rates of cancer, progressive disease and suicide. Post mortem examination is rare, even when bodies are willed to science, due to lack to systems to support these requests.</p> <p>The AHRQ Report must address the above issues, whether they are within the scope of the project or not, if it is to provide a well rounded unbiased view of ME/CFS.</p>	<p>The scope of this report considered adults only. We have added some information on recovery and natural history as well as limitations and applicability, given that severely homebound patients would not be included in these studies.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 51	General	<p>The AHRQ Report must address the above issues, whether they are within the scope of the project or not, if it is to provide a well rounded unbiased view of ME/CFS. To gain a better understanding of the impact of this illness on patients, I recommend that the following be to the AHRQ writers and the P2P panel members:</p> <ul style="list-style-type: none"> • The Voice of the Patient report issued by the FDA in 2013 • The film, Voices from the Shadows full length film that can be viewed for \$3.00. • The National CFIDS Foundation “In Memoriam” list of people with ME/CFS that have died <p>Finally, President Barack Obama wrote “My Administration is committed to creating an unprecedented level of openness in Government. We will work together to ensure the public trust and establish a system of transparency, public participation, and collaboration. Openness will strengthen our democracy and promote efficiency and effectiveness in Government.” Where is the transparency, openness and encouragement of public participation in this P2P process? Clearly from recent documents revealed via a FOIA request, there was no desire for that to happen.</p> <p>Acknowledgements</p> <p>I want to acknowledge that parts of my response were based on information posted on the following blog sites: Occupy CFS , Health Rising, and Onward Through the Fog. I wish to thank all of the writers of these blogs for their thorough review and comments on the AHRQ Draft Report.</p>	<p>Thank you – our team of investigators has viewed the video "Voices from the Shadows" and found it a moving and compelling account of patient experiences. We have reviewed the reports you have recommended and multiple other resources to allow the investigators to have a well rounded impression of the condition and the experience of the patient. We have reflected this in our revised introduction.</p>
B Cella	General	<p>ME/CFS is a complex, misunderstood illness. For the panel to be comprised of non-experts reviewing studies and making determinations regarding diagnosis and treatment that know nothing about ME/CFS is absolutely ridiculous.</p>	<p>Thank you for your comments - although the investigators are not experts in ME/CFS, several members of our team are physicians in addition to being experts in performing systematic reviews following scientific methodology. Additionally, we have had an expert in MECFS as part of our research team throughout the process to help inform and guide the team.</p>
B Cella	General	<p>Medical experts in ME/CFS have already adopted the Canadian Consensus Criteria for research and clinical purposes. This entire P2P workshop is a waste of time and tax payers dollars and should be cancelled. Thank you for your attention to these critical concerns that affect all the patients debilitated by this illness, their families and health care providers.</p>	<p>Thank you for your comments.</p>

Commentator & Affiliation	Section	Comment	Response
B Cella	General	Misinterpretation of cited literature. If the panel consists of persons with no prior knowledge of a complicated illness, and some literature reviews included persons with "fatigue" and not ME/CFFS... plus have no understanding of the definitions used for inclusion and exclusion criteria, how can any recommendations be sound?	Although the investigators are not experts in ME/CFS, out members are experts in performing systematic reviews following scientific methodology. Additionally, we have had an expert in MECFS as part of our research team throughout the process to help inform and guide the team.
Michelle Strausbaugh	General	<p>I wish to thank the members of Scientific Resource Center of the Portland VA Research Foundation for their careful efforts in wading through the complex body of research about ME/CFS at the request of the Agency for Healthcare Research and Quality to inform the Pathways to Prevention project on ME/CFS. I agreed with a number of findings in this draft report including</p> <ul style="list-style-type: none"> • suggestions with regard to future research priorities including the consistent use of a single case definition, studies seeking to distinguish ME/CFS from diseases that may present similarly (like depression, fibromyalgia, multiplesclerosis), larger trials with rigorous adherence to methodological standards, patient-centered outcomes in interventional studies such as quality of life, work and/or school attendance, and time spent supine, and designating PEM, neurocognitive status, and autonomic function as essential features to be studied in all future studies • its attempt to examine the reporting -- or not reporting -- of harms across all treatment modalities as well as the harms associated with the diagnostic label of "chronic fatigue syndrome," • its conclusion that definitions of ME/CFS that require symptoms of Post-Exertional Malaise (PEM), neurological impairment, and autonomic dysfunction represent a group of patients with greater illness severity, • its designating the Oxford definition as especially prone to including patients who may not have ME/CFS and would thus make study results unreliable and create even greater confusion in the evidence-base • that lack of subgrouping of patients has been a significant barrier to understanding who will respond to treatments and has contributed significantly to diagnostic confusion • that there is little to guide clinicians when there is diagnostic uncertainty • that the quality of the evidence base is poor due to small sample sizes, lack of adequate blinding, and the wide variety of methods used to measure outcomes and randomize study participants (if randomization occurred at all) • that, on the face of it, an examination of the evidence-base will suggest that CBT and GET show benefit in self-reported measures of fatigue, function, and global improvement 	Thank you for your encouraging words.

Commentator & Affiliation	Section	Comment	Response
Michelle Strausbaugh	General	<ul style="list-style-type: none"> there were nearly as many papers published on multiple sclerosis in the last year as indexed by PubMed (4529) as have been published on chronic fatigue syndrome since 1987 (5346); this is a shocking level of research neglect for a disease that, while it is true that MS has been a discreet medical entity since the late 19th century(3) and CFS has only been so since the mid-1980s, affects at least one million Americans, involves substantial morbidity and at potentially substantial cost to the US economy; while it is beyond the purview of the Evidence Review to examine and discuss federal funding policy of disease, it cannot be overstated how the paucity of funding for ME/CFS has impacted the current evidence base that has, in turn, created the current confusion about diagnosis and treatment of ME/CFS and I implore the study authors to include a discussion about how this dearth of funding has negatively impacted the evidence base. 	Thank you for your comment - unfortunately funding policies and practices is beyond the scope of this report and our authority.
Michelle Strausbaugh	General	there has also been largely anecdotal concern expressed by advocates and ME/CFS researchers doing biomedical research that NIH has not taken ME/CFS as seriously as would be expected for a disease with its prevalence and severity. The Special Emphasis Panel reviewing grant proposals for ME/CFS research has been singled out at times for showing a sustained and significant bias in favor of behavioral studies (4), most likely due to a lack of knowledge of the disease (which the NIH vigorously denies saying the problem is that there are not enough proposals and/or that the proposals are not of an acceptable quality); any systematic evidence-based review would by its very nature eschew anecdotal reports, but it may be worth considering what potential forms of acceptable evidence there might be about potential bias in how public funds have been distributed in ME/CFS given the preponderance of behavioral studies	Thank you for your comment - unfortunately funding policies and practices is beyond the scope of this report and our authority.
Michelle Strausbaugh	General	while women are well -- if not overly -- represented in the studies included in this draft evidence review, given that ME/CFS is a disease of mostly nonspecific symptoms, that it lacks basic clinically validated biomarkers, that it is more prevalent among women, and that women's health complaints have historically been discounted as "psychosomatic" or "hysteria" by traditionally male-dominated medicine(5), the preponderance of behavioral studies in the ME/CFS evidence base may represent a form of gender bias in which research favoring psychogenic etiology has been systematically favored over biomedical research	Thank you, noted.

Commentator & Affiliation	Section	Comment	Response
Michelle Strausbaugh	General	As the authors of this report and it future Pathways to Prevention panel-member readers well know, at the end of the day this systematic evidence review is not about science for science's sake. It is not a mere intellectual exercise. It is not simply an analysis of mythically value-free facts. It is about how to best inform the decision-making of a variety of "stakeholders" from policy making politicians and bureaucrats to health care providers all for the benefit of the patient. Many of these ME/CFS patients are providing comment on this draft evidence review because they are desperately ill, angry that so very, very, very little has been done to alleviate their suffering, and have almost all felt at one time or another that science and evidence based medicine are used in an authoritarian way to invalidate their experience of their illness. Please remember the variety of ways this evidence review will impact patients in very real ways -- both harmful and helpful.	Thank you for your thoughtful comments. In no way are we attempting to invalidate any patient's experience of their illness. Instead, it is truly our goal to review what evidence is available and to inform the P2P about limitations, applicability, and areas of focus for future research.
Lisa Petrison	General	ME/CFS and Medical Abnormalitis Medical Research - list of references (p11-183)	Thank you for this very comprehensive reference list. The focus of our report was on the diagnosis and treatment of the syndrome of ME/CFS rather than individual symptoms. As such, it was beyond the scope to review theories of etiology and diagnosis of specific symptoms.
Public Reviewer # 43	General	(list of articles from internet from the past month)	Thank you for taking your time to aid in our review. We have reviewed the list of articles, but none of these studies met our inclusion criteria.

Commentator & Affiliation	Section	Comment	Response
Solve ME/CFS Initiative and Research Advisory Council	General	<p>General Comment</p> <p>Even though the review points out the lack of coherence in the field and the absence of high quality clinical trial data, this systematic review would be greatly improved and the field would benefit from an acknowledgement and citation of the substantial body of etiology and biomarker research that can in fact provide clues to diagnostic criteria and potential identification of ME/CFS subtypes. For example, all of the studies that attempted to objectively assess the autonomic nervous system and sleep disturbances (using polysomnography for example) were excluded from this review and not used to address Key Question 1. The same is true for the many important endocrine, neurology and immune studies that have been conducted in an attempt to identify subtypes as well as understand pathophysiology. While these studies may not meet comparative effectiveness review criteria, they are important steps and do provide important clues that could be used to model ME/CFS and inform further fruitful areas of study – including the identification of diagnostic criteria. This seems to be the “Catch 22” for ME/CFS; little funding resulting in small studies of heterogeneous populations. Even still, biological signals do appear to be emerging from some of the clinical trials that were directed at possible etiology (e.g., rintatolimod) and biomarkers such as heart rate variability.</p>	<p>Thank you for your comment. We agree that this work may provide fruitful areas for future study; however, it is not yet at a level of scientific rigor to aid in the diagnosis of the syndrome of ME/CFS. Systematically reviewing the etiology of ME/CFS was beyond the scope of this report.</p>
Lisa Petrison	General	<p>In addition, a list of research studies looking at the physiological abnormalities that have been found in studies of patients qualifying for CFS or ME diagnoses follows. I request that these studies all be considered in any literature reviews that the NIH may conduct.</p> <p>In particular, this study is about the Lake Tahoe cohort, was published in a prestigious journal and was authored by respected researchers. I therefore request that it not be overlooked in the consideration of this disease.</p> <p>Buchwald D, Cheney PR, Peterson DL, Henry B, Wormsley SB, Geiger A, Ablashi DV, Salahuddin SZ, Saxinger C, Biddle R, et al. A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpesvirus type 6 infection. <i>Ann Intern Med.</i> 1992 Jan 15;116(2):103-13. PMID: 1309285</p>	<p>Review of the etiology as well as a review of the diagnosis of individual symptoms of ME/CFS was beyond the scope of this review. For diagnosis, we included studies with a comparator group with the goal of diagnosing the syndrome of ME/CFS and provided some measure of concordance or accuracy. We have discussed the limitations of this in the setting of having no universally accepted reference standard and followed AHRQ methods guidance in reporting.</p>

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Public Reviewer #10	General	While not overflowing with praise for the research around ME/CFS, I still do not believe that the draft report was sufficiently critical, or that you have been able to take the time to do the reading and thinking necessary to write a worthwhile report on this difficult topic. I am concerned that this process is being rushed, and that more time and involvement from patients will be needed in order to avoid this being another semi-thought out piece of work that serves to make life worse for patients. Trying to apply similar methods to writing a report on ME/CFS that one would use for a condition that could be reliably diagnosed, and for which treatments could be either objectively assessed or tested under blinded conditions, is not going to work. This report will need to make important moral and political judgments in complicated and uncertain areas, and cannot pretend that the peer reviewed literature in this area already includes the most important thoughts and opinions - attempting to do so will lead to yet more problems.	Thank you for your comments. The purpose of the report is to present the evidence from existing scientific research and to identify future research needs.
Public Reviewer # 38	General	discussion of overlapping syndromes and comorbid conditions	Thank you for your comments regarding various comorbidities, and your thoughts on the underlying causes.
Public Reviewer # 1	General	<p>It is evident that the authors have devoted considerable time and attention to what is a very complicated area. Many of the suggestions that have been made in the report for ways of improving the data and studies for future evidence reviews will be helpful.</p> <p>Nevertheless, there are a number of areas in the report that require further analysis, additional data and in some cases complete rethinking. The comments that follow are not comprehensive.</p> <p>In preparing these comments reference has been made to the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (CER's) including chapter 5 (Finding evidence for comparing medical interventions), chapter 7 (Avoiding Bias in the Selection of Studies), and chapter 8 (Selecting Observational Studies for Comparing Medical interventions). These chapters clearly demonstrate that, even when great care is taken in preparing these CERs, there are always areas where questions will arise (including the search strategies employed, the studies which are selected and the inclusion and exclusion criteria) – and indeed, these are some of the areas where concerns have arisen. Comments are bolded and in general precede the discussion. Quotes from the evidence report are in italics.</p>	Thank you, noted.

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Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	General	The Review noted a number of limitations on the evidence base including: that important studies may not have been identified; that other diagnostic testing studies may provide further insight into identifying patients with ME/CFS; that treatment studies shorter than twelve weeks were not included; that outcomes for symptoms other than fatigue were not included; that published studies may have been affected by conflicts of interest or bias; and that studies were generally of poor quality. We agree that all of these are serious limitations of this Review.	Thank you for your comment. We would argue that these are serious limitations to the current literature base to inform the diagnosis and treatment of ME/CFS rather than a limitation of the review. One of the tasks is to highlight where future research is needed and we have expanded this section accordingly.
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	General	The Review failed to acknowledge that poor study quality is largely a result of the low levels of research funding available. It must be acknowledged as a factor affecting the evidence base. The ME evidence base cannot be properly assessed without understanding this critical limitation. The Review correctly noted, “treatment of ME/CFS often involves multiple concurrent therapies” but also claimed that the Review’s “interventions and comparators represented most of the therapeutic modalities commonly used in clinical practice.” This is not true. Treatments used for ME patients include a number of medications and therapies excluded from the review including immune modulators, beta blockers, antihypotensives, antidepressants, antivirals, antibiotics, antifungals, stimulants, pain medications, sleep medications, IV saline, and manual physical therapy. The protocol used for the Review excluded almost all of this research. The Evidence Review must explicitly acknowledge this weakness in the applicability of its findings.	Thank you for your comments. Funding issues are beyond the scope of this review or our jurisdiction. Given the breadth of symptomatology associated with ME/CFS, the focus of the systematic review was decided in consultation the Working Group--the focus is on the syndrome of ME/CFS rather than individual symptoms, except for the universal symptom of fatigue.
Helmfrid et al	General	We hereby submit the following text as a comment to the AHRQ Draft Systematic Evidence Review on Diagnosis and Treatment of ME/CFS. We apologize for the fact that our English is somewhat poor (it is not our first language) and hope that the issues we raise will nonetheless be taken into consideration. Sten Helmfrid (sten.helmfrid@bredband.net), Köpenhamng 24, 16442 Kista, Sweden Britt-Marie Thurén Anne Örtegren Methodological problems in studies of cognitive behavioral therapy and graded exercise therapy as treatments for ME/CFS Cognitive behavioral therapy and graded exercise therapy are sometimes recommended as treatments for ME/CFS. The underlying treatment model aims	Thank you for your thoughtful comments. We have highlighted the limitations of these studies, including a lack of subgroup analysis and generally poor reporting of harms. We have reported objective measures when available (actometer results, 6-minute walking test) but have highlighted that these objective measures were also poorly reported. Some of the subjective tools have been validated in the ME/CFS population (see Appendix J of the report) but we do think that future evaluation of objective

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		<p>to change the patient's thoughts about the illness in order to enable them to recover by means of exercise. There are studies that claim positive results of these treatments, but they have serious methodological shortcomings. Objective data are lacking, and the selection of patients is not clearly defined. Negative physiological consequences of exercise have been shown in other studies, and independent evaluations by patient organizations confirm these negative consequences. Therefore, patients with ME/CFS should be advised against cognitive behavioral therapy and graded exercise therapy according to this model.</p> <p>Introduction ME/CFS – also known as chronic fatigue syndrome – is a severe illness that can be debilitating [1]. The World Health Organization (WHO) classifies it, since 1969, as a neurological illness [2]. The etiology and pathogenesis are unknown, but immunological and autonomous abnormalities, neuroendocrine dysfunction, anomalies in the brain and in the functions of mitochondria as well as cognitive impairments have been demonstrated in ME/CFS patients [3].</p> <p>There is no effective treatment for the illness. During the 1990s a group of British liaison psychiatrists – the so-called Oxford school – presented the hypothesis that ME/CFS patients misinterpret signals from their body. Their “abnormal illness beliefs” are to be changed by means of cognitive behavioral therapy (CBT). This therapy is often combined with graded exercise therapy (GET), in which patients increase their activity levels according to a set schedule in order to recover through exercise. GET must not be confused with pacing, in which the patient learns to balance rest and activity and to be attentive to body signals.</p> <p>A number of studies have been published on cognitive behavioral therapy and graded exercise therapy for ME/CFS patients, for example the British PACE study from 2011 [4], which attracted media attention. The results are not unanimous, but several studies claim positive treatment results. However, these studies are seriously flawed and have been harshly criticized by researchers, clinicians and patient organizations [5–12]. This article reviews the methodological shortcomings and shows that CBT and GET according to the Oxford model do not give any positive effects for patients with ME/CFS; but may instead cause a deterioration of their condition.</p> <p>Lack of objective data in the studies The treatment results in the studies of cognitive behavioral therapy and graded exercise therapy have usually been evaluated by means of patient-reported surveys, where the patients themselves report their health status along a given scale [4]. It is well known that there is a placebo effect in subjective reports. The placebo effect has many causes, but among other things it is influenced by the attitude of the researcher. For this reason the systematic deviation can be expected to be large in the case of cognitive behavioral therapy according to the</p>	<p>measures will help to advance this field of study. Critical review of the etiology or the physiological theories pertaining to therapeutic effectiveness was beyond the scope of this report. We have expanded our discussion of the limitations, applicability, and recommendations for future research.</p>

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		<p>Oxford model, since the treatment aims at convincing the patients that the method works.</p> <p>Double blind testing is not possible in the case of psychological intervention, but the activity levels of patients can be measured with a so-called actometer, a device the size of a wristwatch that is attached to the wrist or the ankle. It is important that activity be measured continuously over time, since ME/CFS patients tend to compensate for increased activity in one area with decrease of other activities. In most published studies of cognitive behavioral therapy and graded exercise therapy, objective measurements of activity level before and after treatment have not been included. This makes it difficult to assess how the functional level of the patients has been affected.</p> <p>Objective measurements have only been presented on a few occasions. In one publication, a Dutch group reviewed three earlier studies of cognitive behavioral therapy and gathered data from actometers retroactively. The analysis showed that there had been no objective increase of patient activity level, even though the patients had reported a subjective decrease of fatigue in the surveys [13]. In another publication, neuropsychological test results before and after CBT treatment were compared. The self-reported cognitive functional impairment decreased with CBT, but objective test results remained unchanged [14].</p> <p>Some studies have attempted to evaluate the treatment results of cognitive behavioral therapy and graded exercise therapy in a more objective manner, but the data gathered have been insufficient. In the British PACE study, the distance that patient managed to walk in six minutes was measured, and a minor increase was shown for the CBT and GET groups [4]. However, the walking test is a blunt measure of objective improvement, since it is not possible to control how much of an effort the patients make. Nor was the total activity level registered with actometers, so it is impossible to determine whether the general functional level of the patients improved. In a Dutch study of internet-based CBT for young people, school attendance was registered [15]. But study results were not measured, nor was there any check on whether increased attendance was compensated by a decrease in other activities. It is therefore not possible to reach any firm conclusions about changes in the functional level of the patients.</p> <p>The final result of the walking test in PACE was an average of 354 meters for patients treated with CBT and 379 meters for the participants in the GET program. It should be noted that this is far from the reversal of the condition that the researchers claim is possible. For the sake of comparison, we can mention that a healthy person manages about 600 meters in a walking test. The limit where a lung transplantation is recommended for a person with lung disease is 400 meters [16], and in one American study of elderly persons with chronic heart failure, the most seriously ill group attained a result of 402 meters [17].</p> <p>Ill defined patient groups</p>	

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		<p>Another problem is that in many studies the diagnostic criteria and therefore also the selected patient groups have been unclear. Centers for Disease Control and Prevention (CDC) published the first criteria for chronic fatigue syndrome in 1988 after an outbreak in Lake Tahoe and introduced the concept of Chronic Fatigue Syndrome (CFS) [18]. The criteria were updated in 1994 [19], and this set of criteria – sometimes called “the Fukuda criteria,” after the first author – is the most commonly used in scientific publications about ME/CFS. According to these criteria, the disease is not considered just a form of long-lasting fatigue. Apart from chronic fatigue, patients must show four further symptoms from a list of eight symptoms that are neurological and immunological in character.</p> <p>In 1991, the Oxford school published its own criteria for CFS, even though the name CFS was already in use and defined by the Fukuda criteria. The so-called Oxford criteria only require long-lasting severe fatigue [20], although the patients may also have other symptoms. Thereby a much larger and much more heterogeneous patient group is defined than that of the Fukuda criteria. Among other things, many patients with psychiatric diagnoses are included.</p> <p>In 2003, an expert committee commissioned by Health Canada, prepared a consensus document about ME/CFS and published a new and stricter set of criteria, now usually called “the Canadian consensus criteria (CCC)” [21]. The purpose was to define a more homogeneous patient group. Among other things post exertional malaise (PEM) was emphasized as a mandatory symptom. Along with PEM, patients must show a large number of neurological, immunological and endocrine symptoms. This set of criteria is used by the International Association for CFS/ME (IACFS/ME) [3] and is recommended by most biomedical researchers in the field.</p> <p>Evaluation and comparison of treatment studies of ME/CFS have been hindered not just by the many different sets of criteria but also by the fact that many authors have “operationalized” the diagnostic criteria. Usually operationalization means that the criteria are reformulated in order to make it possible to apply instructions in an experiment. In many studies of treatment with CBT/GET, the concept of operationalization has been twisted or some of the requirements of the criteria have been eliminated, all of which produces uncertainty as to whether the results really reflect the correct patient group according to a certain set of criteria. Most early studies of CBT/GET were based on the Oxford criteria [22] or on operationalized Fukuda criteria [23]. More recently, studies using the complete Fukuda criteria have also been published [24]. It is not clear whether the results for a large heterogeneous patient group can also be assumed to be valid for a more strictly defined group, for instance patients that comply with the Canadian consensus criteria (CCC). One study from British primary care shows that the probability of a positive treatment result with CBT and GET in the case of long-lasting fatigue substantially decreased if the patients complied with criteria for</p>	

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		<p>ME/CFS (in this case the Fukuda criteria) [25].</p> <p>In the PACE study, the Oxford criteria were used, but alongside this a comparison was made with the results for patients that simultaneously complied with the so-called London criteria [26] and the Reeves criteria [27]. Unfortunately, it is difficult to draw any secure conclusions from this comparison: only subjective results were included, and the strictest definition, the Canadian consensus criteria, was not used.</p> <p>Physiological abnormalities indicate activity-induced deterioration</p> <p>A number of studies indicate that activity causes a worsening of the condition of ME/CFS patients. A research team in the USA, led by Christopher Snell, studied the absorption of oxygen in ME/CFS patients during repeated exercise tests. The tests were carried out with an interval of 24 hours. In the first test, the ME/CFS patients demonstrated normal values, but, unlike controls, in the second test they showed a clearly reduced capacity of oxygen absorption, both at maximum level (VO₂ peak) and at the anaerobic threshold [28]. These results are completely compatible with the post-exertional malaise of which patients often complain, and which is a mandatory symptom in the Canada consensus criteria. Similar results have recently been published by another American group led by Betsy Keller [29]. Increasing evidence indicates that dysfunctions in the metabolic system related to the switch between anaerobic and aerobic energy production is causing the post-exertional malaise present in ME/CFS [30]. Patients should especially avoid "oxygen debt". The graded exercise therapy recommended by the Oxford school is aerobic. The results of the Snell group underline the importance of differentiating between different types of chronic fatigue. Fatigued patients with a primary depression improve with aerobic exercise, whereas in ME/CFS patients it induces deterioration, and if the ME/CFS patients also suffer from a secondary depression, their depression is simultaneously worsened [30].</p> <p>An American study has demonstrated changes in gene expression of ME/CFS patients during 48 hours after exercise [31]. A British study has shown elevated concentrations of the inflammatory cytokine TNF-α three hours and three days after exercise [32].</p> <p>Patient evaluations demonstrate problems with CBT and GET</p> <p>Over time, patient organizations have repeatedly evaluated different forms of treatment through questionnaires. There are data available from ten independent surveys carried out in four different countries with more than 13700 patient responses [33,34]. The survey results confirm that graded exercise involves great risks for deterioration of health in ME/CFS patients. More than 4600 patients had tried this kind of treatment and altogether 52% reported that they felt worse. The largest survey was done by The ME Association in the UK. In a comparison of various therapies, graded exercise therapy showed the lowest proportion of patients who had experienced improvement and the highest proportion that had</p>	

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		<p>experienced deterioration [35]. More than 56% of the patients got worse because of the treatment, and 33% reported that they had gotten much worse. Both in the case of graded exercise and that of cognitive behavioral therapy, a lower share of the patients reported improvement and a larger share reported deterioration than in the case of homeopathic treatments. Homeopathy is currently considered a pseudo-science, and the results of treatments according to this method therefore indicate the level of placebo effect. The same pattern was seen in a Norwegian patient survey [34].</p> <p>In the PACE study, the risk for deterioration in graded exercise therapy was studied. No relapses were reported and the authors concluded that the treatment is safe. This result stands in sharp contrast to all patient surveys. However, it is not possible to determine whether the patients increased their activity level according to the protocol of PACE, since actometers were not used. The walking test showed that the patients could walk 379 meters in six minutes, which is far from the goal of recovery through exercise. If the level of activity is increased, the risk for a relapse will increase. This can explain why graded exercise therapy so often leads to deteriorated health when put into continued practice. Therefore the conclusion that graded exercise therapy is a safe treatment is highly questionable.</p> <p>The underlying theory lacks theoretical support</p> <p>The Oxford school treatment model is based on two hypotheses, fear avoidance theory and deconditioning and exercise intolerance theory. The first one makes the assumption that patients are afraid of activity and avoid effort, and that this behavioral pattern perpetuates the symptoms. The second hypothesis suggests that symptoms are caused by deconditioning, due to the patients' low level of activity. The condition can be reversed by changing the thought and behavioral patterns of the patient [4].</p> <p>These hypotheses seem dubious already at first sight. The presumed fear of activity disagrees with the push-crash cycles, which both patients and doctors report [36]. If deconditioning were to cause ME/CFS symptoms, as the second hypothesis claims, similar symptoms should be observed in persons who are inactive for other reasons, for instance persons who are put in plaster for a long period of time or prisoners in isolation. Nor has any reversal of ME/CFS through modified thought patterns been demonstrated, neither in PACE nor in any other study. The hypotheses are thus contradicted by the research results of its proponents.</p> <p>The Oxford school has not been able to present any theoretical foundation for their ideas, although some attempts were made. Vercoolen et al published a structural equation model for ME/CFS, concluding that behavioral and cognitive factors contribute to the perpetuation of the illness [37]. However, the results do not justify such a conclusion. Structural equation models can be used to test</p>	

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		<p>causal hypotheses, but not to validate causal conclusions [38]. It is not possible to determine what is cause and what is effect among the biological, behavioral and cognitive factors present in ME/CFS without an understanding of underlying mechanisms; and this is not included in the model. Furthermore, Vercoulen used a heterogeneous group of patients. When the results were tested by other researchers, the model showed poor agreement for ME/CFS patients, but good agreement for patients with depression [39]. Harvey and Wesely have published a "model for understanding the etiology of CFS" [40]. The model consists of a figure showing how various factors interact in ME/CFS, but the authors do not describe any underlying mechanisms and do not explain how one should determine what is cause and what is effect in any given interaction. This "model" is therefore not an explanatory model in the scientific sense, but just a diagram of unfounded assumptions made by the authors.</p> <p>Conclusions</p> <p>A number of studies have been published on cognitive behavioral therapy and graded exercise therapy according to the Oxford model for patients with ME/CFS, and some of the studies claim that a modest but statistically significant improvement is obtained. However, when all the evidence is considered, there is good reason for questioning the usefulness of treatment with these methods and for being cautious about the risks for harm. No objective improvements have been demonstrated in any of the studies. The only objective evaluations that have been carried out of CBT indicate that the activity level and the neuropsychological functional level have not improved. Patient groups have been unclearly defined in many studies. It is highly uncertain if research on patients with general long-lasting fatigue is also representative for patients with neurological, immunological and endocrine symptoms along with fatigue.</p> <p>Delayed physiological abnormalities have been shown in ME/CFS patients after exertion, for example changes in gene expression and decreased absorption of oxygen. This is confirmed by results from extensive independent patient surveys, demonstrating that a large proportion of patients have experienced deterioration in health – in the case of graded exercise therapy more than 50 %. The proportion of patients who have experienced improvement is on the level of the expected placebo effect.</p> <p>There is no theoretical basis for cognitive behavioral therapy and graded exercise therapy according to the Oxford model. The underlying assumptions are contradicted by the Oxford school researchers' own results.</p> <p>The usefulness of treating ME/CFS patients with cognitive behavioral therapy and graded exercise therapy according to the Oxford model cannot therefore be considered as based on evidence, and the risk for negative consequences means that health care professionals and patients should be advised against these forms of treatment. However, patients should be encouraged to engage in physical</p>	

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		<p>activity to the degree the disease allows, for example using pacing in order to find a balance between activity and rest. Cognitive behavior therapy with the aim to assist patients in coping with a serious disease can also be useful in many cases. Usually, none of the methodological shortcomings discussed above appear in literature reviews or Cochrane publications. When health care authorities produce state of knowledge reviews, they normally use such compilations, and for this reason they often turn out to be misleading. It is vital to engage biomedical expertise and to critically review the original studies, as well as peruse the debate following their publication, for example in the form of letters to the editors in medical publications.</p>	
Public Reviewer # 40	General	<p>I have had two goals in taking many hours to write these comments. I wish first to forward and pursue the interests of citizens of the United States, in respect of the AHRQ Evidence Review as contracted for and specified by employees of the National Institutes of Health, an agency of the executive branch of the U.S. government.</p> <p>To this end, I wish secondly to make known for the benefit of the Review's authors and revisers the historic events dating from 1984 to the present which resulted in construction of the name "Chronic Fatigue Syndrome" and its application to the Incline Village, Nevada outbreak of the disease formerly known as Myalgic Encephalomyelitis and designated at 93.3 under neurological diseases by the WHO. This history also encompasses the confounding and spoilage which occurred to this AHRQ Evidence Report by misapplication of the name "Chronic Fatigue Syndrome" in the United Kingdom to altogether different non-biomedical psychological phenomenon which have already fated British patients to mistreatment and now threaten Americans should their incorporation into the AHRQ evidence review prevail.</p>	<p>We have been very grateful to individuals like you who have shared their breadth of knowledge of ME/CFS through history as well as the experiences associated with the name of CFS. At the outset of this review, the intent was not to address the subject of etiology or pathophysiology of the condition but rather to focus this report on diagnosis and treatment of the syndrome. We recognize that this task is made more challenging due to the lack of a universally agreed upon definition and the differences that exist between definitions. We have highlighted this in our report.</p>
Public Reviewer # 53	General	<p>The AHRQ has left out the stakeholders and the experts: the patients with ME and the experts in the field. Regardless of the AHRQ staff's training and professionalism, the brain trust that has developed treating patients and studying the root causes of ME for three decades cannot be ignored. They are the only people with the expertise to lead this process. The AHRQ can't achieve its goals without engaging them.</p>	<p>The team of investigators sought to first inform themselves of the illness labeled in the literature as ME and/or CFS. We have included on our research team throughout the review, a local expert in ME/CFS who has been studying the disease for several decades. Additionally, we have included experts and patients on our Technical Expert Panel that helped guide the direction of the review. We have opened the report up for public comment and are very appreciative of the breadth of responses we have received, addressing all of these comments as able.</p>

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Public Reviewer # 53	General	Luckily, the AHRQ effort is still early in its process; it can correct the problems and launch at a later date to arrive at the helpful outcome that is intended. To do so, the AHRQ must redefine its objectives. As I have noted earlier, the first and most significant step is developing an accurate statement of initial starting assumptions: what defines ME. Then engage the ME experts, the brain trust, to participate in forming the starting assumptions. Then you can examine the health anomaly that is ME with a lens that allows the unbiased development of root causes, that take into consideration all the relevant and critical disciplines, so that an accurate initial set of assumptions can be assembled and applied to the proper population. My wife is part of that population; please keep her alive.	Thank you for your comments. We have reviewed and highlighted the differences in the various case definitions. In response to public opinion such as yours, we have expanded our discussion of recommendations for future research, including a decision to embrace one case definition to help direct this research.
Public Reviewer #11	General	We are currently lacking good evidence that biopsychosocial rehabilitative approaches are more effective than placebo, Chakra healing, or any other intervention that leaves patients wanting to be positive to their therapist and that is assessed via self-report measures. It is important that this is made clear so that patients are able to make informed decisions about their own medical care and their own lives.	Thank you for your comment. We agree that there is need for more research.
Public Reviewer #12	General	"Given the breadth of symptoms in ME/CFS, we a priori elected to not review symptom related outcomes except for fatigue." (Draft review, es30) A problem with this is the we do not have a reliable measure for 'fatigue'. Much trouble has been caused by researchers seeming to just assume some fatigue questionnaire reliably captures the symptom most troubling to patients with ME/CFS, even when assessing biopsychosocial interventions specifically intended to alter patient cognitions.	Thank you, noted.
Bianca Lindstrom Anneli Magnusson Lars-Eric Magnusson Benita Meriaux Anton Meriaux Mireille Edgren Hans Edgren Åsa Kleberg Sven-Erik Johansson Vera Bengtsson	General	I fully support the comment Factual and Conceptual Errors in the Executive Summary of the Draft Comparative Effectiveness Review "Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)" Raise Questions of the Review's Fitness for Purpose, submitted by Public Reviewer # 39 October 3, 2014. Further, I fully support the comments submitted by Jennifer Spotila, JD, et al. on October 18, 2014. Careful consideration of the above issues raises legitimate concerns about whether this Review will produce good science and sound recommendations. I hope you will give my concerns a fair hearing, and that these issues are addressed before the evidence review is issued in its final form.	Thank you, noted.
Public Reviewer # 53	General	Comments on the AHRQ Draft Comparative Effectiveness Review on the Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) "HOLD! HOLD! HOLD!" This is what everyone in the chain of those responsible	Thank you kindly for your letters and for sharing your stories with our team. We included patients and experts as members of our Technical Expert Panel,

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		<p>for mission assurance say in my profession of launching satellites into space when there is a problem detected with the launch vehicle, the satellite, the software, the ground systems, anything that could possibly impact the orbital injection of the payload. Calling HOLD HOLD HOLD can happen even in the last seconds of a count-down, and is the right thing to do even though it will disappoint people high up in the chain of command and delay agendas and timelines. Human safety and mission assurance far exceed all that. We don't hold a launch until the anomaly is resolved, regardless of the political fallout. We are given this authority because it is the right thing to do.</p> <p>It may be easy to understand that lives are at stake when a rocket—even an unmanned one—is launched; should it go off course, human lives are at risk. Your task is not dissimilar. As the husband of a person with ME*, I am calling HOLD HOLD HOLD after studying the AHRQ Draft Systematic Evidence Review on Diagnosis and Treatment of ME/CFS. It is unsafe to proceed with the plans as they have been designed, for the current path will lead to less efficacy and greater harm for the proposed medical and nonmedical interventions to treat ME in adults.</p> <p>I am professionally trained to review engineering data, uncover anomalies and develop resolutions. I ensure the anomaly is driven to root cause, and evaluate go-forward plans for efficacy and thoroughness. A collaborative environment of all stakeholders and experts is the only way this works. Our engineering review boards include people with knowledge, experience and insight into how the system works and what needs correction to ensure the system functions as designed.</p> <p>The AHRQ has left out the stakeholders and the experts: the patients with ME and the experts in the field. Regardless of the AHRQ staff's training and professionalism, the brain trust that has developed treating patients and studying the root causes of ME for three decades cannot be ignored. They are the only people with the expertise to lead this process. The AHRQ can't achieve its goals without engaging them.</p> <p>*Endorsing and echoing the comments submitted by Jennifer Spotila et. al., I use the term ME.</p> <p>In addition to excluding the best minds for the task, the AHRQ has ignored the critical disciplines: etiology; immune, cardiopulmonary, neural, and autonomic biomarkers; as well as Post Exertional Malaise that is crucial to defining the illness of ME and differentiating between those who have it and those who are fatigued, even chronically, because of any number of other conditions. Without this distinction the AHRQ does not have a precise population for which to compare studies.</p> <p>Let me illustrate my points with a personal perspective. My wife Carollynn Bartosh has been disabled by ME for more than ten years. She was an ambitious</p>	<p>and strove to attend to their areas of concern and guidance as we prepared our report. Numerous comments surround the debilitating effects of post-exertional malaise or neuroimmune exhaustion that patients experience. We have highlighted that this area of research is essential; however, the purpose of this report was to focus on the syndrome of ME/CFS rather than the individual symptoms that a patient suffers. We looked for any evidence that differentiated subgroups of patients in how they responded to various interventions or how diagnostic methods might vary, but unfortunately found very little evidence that met our predefined criteria. It is our responsibility as independent investigators to strictly report on evidence that is currently available using a pre-defined and structured systematic method. One of the tasks requested was to draw attention to areas where research is lacking and to give our recommendations on where efforts should be placed in order to better guide funding, research, and clinical practice. One recommendation is that patients be stratified based on their baseline symptoms in order to better determine if some interventions are more effective or potentially more harmful for subgroups of the population. This has been difficult for researchers to do in the past given that the studies have mostly been small and thus may not detect a difference even if a difference exists. Another recommendation is that studies perform sensitivity analyses to determine if differences in outcomes exist between patients who meet different case</p>

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		<p>professional and a model of good self care; she was the last person I would have thought was headed for a chronic illness.</p> <p>When Carollynn got sick, we were fortunate that our GP sent her to Dr. John Chia, an infectious disease specialist and ME clinician/researcher nearby, who measured in her blood elevated, reactivated levels of EBV, HHV-6, Chlamydomphila pneumonia, an enterovirus, and the enterovirus Coxsackie B5. At the time, she was diagnosed with CFS. There have been few treatments to try, mostly off-label uses of drugs developed for other conditions, but we've tried everything. We realized early on that most other doctors think CFS is a form of depression, that they thought "fatigue" was her big complaint despite witnessing her symptoms and diagnosing several other bio-organic conditions commonly concomitant with ME: Postural Orthostatic Tachycardia Syndrome (POTS), Neurally Mediated Hypotension (NMh), interstitial cyctitis (IC), an IGG deficiency, and a slew of serious allergies and sensitivities to foods and medicines. The state of medical practice meant that we had to learn as much as we could about the science of her condition to best help her.</p> <p>Meanwhile, we knew that activities my wife loved and might feel well enough to enjoy on one day, like a family birthday gathering or a nice hike in the local hills, could lead to an exacerbation of all of her flu-like symptoms, symptoms that correspond to one or another of that cocktail of pathogens Chia found, and may render her home-bound for a week or two.</p> <p>In time shingles, Varicella Zoster Virus/VZV, came into the mix for her, a very atypical presentation for the general public but typical of someone with a severely compromised immune system, such as with HIV, and for five years she's had break-through flare ups over most of her body despite remaining on the highest acute dose of antivirals. She has VZV-related hearing loss in one ear and sees her ophthalmologist every few months to keep tabs on the shingles she's had in her eyes.</p> <p>The exceptional memory she used to have is spotty at best. The company she worked for before she got sick would say she was the glue that held their operations together, and it was her memory that made us marvel, her ability to hold multiple and complex threads of activities, internal and external relationship networks, working budgets, agendas, and plans. The person who could tell me what I was wearing on a particular outing four years ago can't remember if she's given our cat his daily medicine without leaving a trail of visual cues. When we make dinner together we sometimes can't talk if we're following a recipe because she can no longer hold an instruction in mind while hearing about my day.</p> <p>Before Carollynn became sick she used to drag me on vigorous morning walks four days a week, training for our vacations hiking at altitude. She loved to garden and prided herself in doing all the heavy work, alongside the big guys we'd hire to help, too, insisting that it was good exercise and escape time from her busy</p>	<p>definitions of ME/CFS.</p>

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		<p>professional life. Feeling sick with flu-like symptoms after exercise was one of the first clues to us that something was wrong, and soon, as she become more ill, feeling like that after mental activity as well. Now, after nominal physical or mental activity even on a “good day” she may experience a flare-up of shingles a few days later. Dr. Chia believes that VZV will be resolved when the underlying immune dysfunction of ME is understood and treatments are found. Until then, there are many aspects of her condition that we have little control over. Her mental health, however, is not one of those. Amazingly, she is not also depressed.</p> <p>In 2007, three years into disability, we were thrilled that the leading clinicians and researchers changed the name of the illness from CFS to ME, and soon accepted the Canadian Case Definition with PEM as its central feature. Five years in, we found the Lights' first exercise studies in Post Exertional Malaise the most validating, targeted science to date. We made a flyer from the CFIDS Assoc. webinar materials to share with our doctors, family, and friends—and I have seen every doctor sit up to take notice (see below). We followed the subsequent studies by Stevens, Snell, Davenport, and VanNess into VO2max and anaerobic threshold, applying their subsequent safe exercise protocols with following my wife's heart rate not just during careful laying and sitting exercises but throughout activities of daily living. As an engineer I see that being able to quantify differences between healthy adults and those with ME is a great move forward. As I plotted her daily heart rate, we were not surprised to find the tachycardia typical of ME but also some troubling readings, too, that appeared to be bradychardia.</p> <p>We read more studies about cardiac anomalies in ME such as Bell's low blood volume study and Peckerman's on heart failure, Jason's on causes of death in ME—studies from ten, fifteen years ago that should have received more attention, that should by now be part of standard knowledge for treating ME patients.</p> <p>When the cardiologist who performed the tilt table test in which Carollynn fainted told us that he “doesn't believe in ME/CFS,” we went to a different doctor. He performed a 48-hour Holter monitor test. Through it we learned that what appeared to be bradychardia is arrhythmias, yet he would not engage any of the literature about blood volume that could be related and said that anti-depressants are sometimes prescribed for this condition.</p> <p>After we brought these studies of low blood volume to the attention of our supportive GP, he was able to authorize four weekly infusions of IV-saline for her—not because of her ME diagnosis but because of POTS--resulting in my wife's POTS and NMH numbers improving dramatically and the arrhythmias abating. Her heat intolerance, which should have been problematic during the worst heat wave of the year, also abated. Because of delays in insurance</p>	

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		<p>authorizing further infusions, it has been two weeks since her last one. We can see in her daily heart rate charts that she has lost all the ground she gained. We hope the authorization for continuing the infusions will be forthcoming, but we are concerned they may not be approved because of the lag between scientific discovery and clinical practice.</p> <p>All of the studies that validated our experiences, corroborated her symptoms, gave us criteria for measurement and the ability to document change, that brought some relief and a basis for looking for improvement over time in this story have been left out of the AHRQ review. Those studies as well as Chia's delving into "smoldering viruses" and every other study by researchers related to pathogens and post-viral syndromes, possible root causes, and other studies that the current AHRQ have found too small for inclusion are precisely the ones that physicians in general practice need to know about—now, even before the whole nut of ME has been cracked—in order to stop harming and begin helping patients. It is faulty review criteria that excludes this most promising science. It needn't be the case.</p> <p>As if it is not enough for patients to languish for years and decades without real treatment options, when doctors have been told by the NIH that ME is the same thing as CFS, only treated with CBT and GET, they do not take seriously the constellation of symptoms that reveal that ME can be fatal. Our friend Hugh, who had been enjoying great improvement in his ME after being disabled for 25 years, went to an emergency room with severe upper abdominal pain. He was sent home with a diagnosis of stomach flu. Two weeks later he went back to the ER and was finally diagnosed in heart failure. By that time, his heart was seriously damaged. The doctors had not driven Hugh's health anomaly to root cause because they lacked the knowledge and direction that should be in place now for patients with ME. Hugh is alive, with a pace maker now, but living at a substantially reduced level of ability and well-being. But how many Hughs are out there? How many have not survived because the protocols are poorly constructed? These are just some of the harms that the system has in place now. And the trajectory of the path the AHRQ has set in motion now will only end up in this same place.</p> <p>This totals up to a NO-GO for launch into achieving the goals of the AHRQ. Luckily, the AHRQ effort is still early in its process; it can correct the problems and launch at a later date to arrive at the helpful outcome that is intended. To do so, the AHRQ must redefine its objectives. As I have noted earlier, the first and most significant step is developing an accurate statement of initial starting assumptions: what defines ME. Then engage the ME experts, the brain trust, to participate in forming the starting assumptions. Then you can examine the health anomaly that is ME with a lens that allows the unbiased development of root causes, that take into consideration all the relevant and critical disciplines, so that</p>	

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		an accurate initial set of assumptions can be assembled and applied to the proper population. My wife is part of that population; please keep her alive.	
Mary Dimmock et al.	General	<p>The issues with this Evidence Review are substantial in number, magnitude and extent. At its root is the assumption that any case definition is as good as the rest, and that studies done on one patient population are applicable to every other patient population, despite the significant and objective differences among these patients. The failure to differentiate between patients with the symptom of subjective unexplained fatigue on the one hand, and objective immunological, neurological and metabolic dysfunction on the other, calls into question the entire Evidence Review and all conclusions made about diagnostic methods, the nature of this disease and its subgroups, the benefits and harms of treatment and the future directions for research.</p> <p>As the Evidence Review states, the final version of this Evidence Review may be used in the development of clinical practice guidelines or as a basis for reimbursement and coverage policies. It will also be used in the P2P workshop and in driving NIH's research strategy. Given the likelihood of those uses and the Evidence Review's claim of broad applicability to all CFS and ME patients, the flaws within this report create an undue risk of significant harm to patients with myalgic encephalomyelitis and will likely confound research for years to come. These issues, more fully outlined in the attached comments, must be addressed before this Evidence Review is issued in its final form.</p>	<p>We erred on the side of being more inclusive with the case definitions as there is no agreed upon gold standard. We sought to evaluate all available evidence on these case definitions. We have expanded our discussion of the limitations, applicability and future research needs sections.</p>
Public Reviewer # 42	General	<p>The PACE trial is given an a study quality assessment of Good There have been many complaints about this trial including an official complaint to the Lancet by Professor Hooper University of Sunderland who states the PACE Trial itself was unethical and unscientific definitions and outcome measures were changed repeatedly data appears to have been manipulated obfuscated or not presented at all so it cannot be checked and the authors interpretation of their published data as moderate success is unsustainable. The Lancet has acknowledged this and stated the erroneous reporting of the trial results must be corrected. I would therefore suggest this study be removed entirely from this review. White PD Goldsmith KA Johnson AL et al. Comparison of adaptive pacing therapy cognitive behaviour therapy graded exercise therapy and specialist medical care for chronic fatigue syndrome PACE a randomised trial. Lancet. 2011;377:9768-82336. PMID 21334061.</p>	<p>Thank you. We have expanded our discussion of the limitations of this and other studies. The quality rating (internal validity) is based on pre-specified criteria and though a study may get a rating of good, the applicability of the study may have limitations. We have expanded on this in the discussion of the studies.</p>
Public Reviewer # 41	General	<p>Additional References Poor mans tilt table testing description Neuroimaging References Neurological Dysfunction in Chronic Fatigue Syndrome Journal of Chronic Fatigue Syndrome The Haworth Medical Press an imprint of The Haworth Press Inc. Vol. 6 No. 34 2000 pp. 5168. Abhijit Chaudhuri DM MD MRCP Peter O. Behan DScMD FACP FRCPSPECT Imaging of the Brain Comparison of Findings in Patients with Chronic Fatigue Syndrome AIDS Dementia Complex and Major Unipolar Depression Richard B. Schwartz Anthony</p>	<p>Thank you for your references. Unfortunately, they do not meet our inclusion criteria for this report.</p>

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		<p>L. Komaroff Basem M. Garada Marcy Gleit Teresa H. Doolittle David W. Bates Russell G. Vasily B. Leonard Holman American Journal of Roentgenology Vol 162 943951 Copyright 1994 by American Roentgen Ray Society. Summary This study shows that CFS ME shares some similarities on SPECT imaging with AIDS Dementia Complex acute changes in radionuclide uptake in the younger population may be caused by inflammatory processes at the cellular or micro vascular level the findings in CFS ME face are consistent with the hypothesis that CFS ME ... results from a viral infection of neurons glia or vasculatureviral infection can provoke neurological dysfunction by interfering with intracellular mechanisms or membrane transport systems or by cerebral hypoperfusion due to vasculitis. It has been known for some time that CFS patients have abnormal blood flow in their brains that is some areas of the brain are not getting as much blood as they should. Dr. Ismael Mena has studied M. E. CFS patients brains using SPECT scans at the University of California Los Angeles where he is a professor of radiology Ismael Mena M.D. Study of Cerebral Perfusion by NeuroSPECT in Patients with Chronic Fatigue Syndrome The Cambridge Symposium on Myalgic Encephalomyelitis 1990 1 2122. Gordon R et al. Cortical motor potential alterations in chronic fatigue syndrome. Int J Molec Med. 1999 4 49399. Proton magnetic resonance spectroscopy of basal ganglia in chronic fatigue syndrome. Chaudhuri A Condon BR Gow JW Brennan D Hadley DM. Neuroreport. 2003 Feb 101422258. Costa DC Brostoff J Douli V Eli PJ. Brainstem hypoperfusion in patients with Myalgic Encephalomyelitis Chronic Fatigue Syndrome. Eur J Nucl Med 1992 19733. Brainstem perfusion is impaired in chronic fatigue syndrome. DC Costa C Tannock and J Brostoff. Quarterly Journal of Medicine December 199588767773 Relationship of brain MRI abnormalities and physical functional status in chronic fatigue syndrome Cook DB Natelson BH. Int J Neurosci 20001071216 Brain positron emission tomography PET in chronic fatigue syndrome preliminary data Tirelli U et al. Am J Med 1998105 3A54S58S Brain MRI abnormalities exist in a subset of patients with chronic fatigue syndrome. Lange G DeLuca J Maldjian JA Lee H Tiersky LA Natelson BH. J Neurol Sci. 1999 Dec 1171137. Chronic fatigue syndrome aetiological aspects. Dickinson CJ. Eur J Clin Invest. 1997 Apr27425767 Brain MR in chronic fatigue syndrome. Greco A Tannock C Brostoff J Costa DC. AJNR Am J Neuroradiol. 1997 Aug187 12659. Relationship of brain MRI abnormalities and physical functional status in chronic fatigue syndrome. Cook DB Lange G DeLuca J Natelson BH. Int J Neurosci. 2001 Mar1071216. Quantitative assessment of cerebral ventricular volumes in chronic fatigue syndrome. Lange G Holodny AI DeLuca J Lee HJ Yan XH Steffener J Natelson BH. Appl Neuropsychol. 2001812330. Immune Function References Evidence for the Presence of Immune Dysfunction in Chronic Fatigue Syndrome. Benjamin H. Natelson Mohammad H. Haghghi and Nicholas M. Ponzio. Departments of</p>	

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		<p>Neurosciences Pathology University of Medicine and Dentistry New Jersey Medical School Department of Psychology Rutgers University Newark New Jersey Clinical and Diagnostic Laboratory Immunology July 2002 p. 747752 Vol. 9 No. 4 1071412X0204.000 DOI 10.1128CDLI.9.4.747752.2002 2002 American Society for Microbiology Low NK syndrome and its relationship to chronic fatigue syndrome. Aoki T Miyakoshi H Usuda Y Herberman RB. Clinical Immunology and Immunopathology 1993 693 25365. A chronic illness characterized by fatigue neurologic and immunologic disorders and active human herpesvirus type 6 infection. Buchwald D Cheney PR Peterson DL Henry B Wormsley SB Geiger A Ablashi DV Salahuddin SZ Saxinger C Biddle R et al. Annals of Internal Medicine 1992 1162 10313. Immunologic abnormalities associated with chronic fatigue syndrome. Barker E Fujimura SF Fadem MB Landay AL Levy JA. Clinical Infectious Diseases 1994 18Suppl 1 S13641. A comprehensive immunological analysis in chronic fatigue syndrome. Gupta S Vayuvegula B. Scandinavian Journal of Immunology 1991 33 319327. Abstract A detailed analysis of cellmediated and antibodymediated immunity was performed in 20 CDCdefined patients with chronic fatigue syndrome CFS and 20 age and sexmatched healthy controls. CD3 CD4 CD8 and CD20lymphocytes were comparable in two groups. Natural killer cells as defined by CD16 CD56 and CD57 antigens were significantly reduced in CFS. A significant increase in the proportions of CD4 ICAM 1 T cells was observed in CFS. Monocytes from CFS displayed increased density as determined by mean fluorescence channel numbers of intercellular adhesion molecule 1 ICAM1 and lymphocyte function associated antigen 1 LFA1 but showed decreased enhancing response to recombinant interferongamma in vitro. The lymphocyte DNA synthesis in response to phytohaemoglobin PHA Concanavalin A Con A and pokeweed mitogen PWM was normal but the response to soluble antigens was significantly reduced. Serum IgM IgG IgA and IgG subclasses were normal. In vivo specific antibody response to pneumococcus vaccine was depressed in CFS. Forty percent of patients showed titres of antihuman herpes virus 6 antiHHV6 antibody higher than that in the controls greater than or equal to 180. These data suggest immunological dysfunction in patients with chronic fatigue syndrome. The significance of these observations is discussed. Immunological abnormalities in patients with chronic fatigue syndrome. Tirelli U Marotta G Improta S Pinto A.Scandinavian Journal of Immunology 1994 406 6018.Low NK syndrome and its relationship to chronic fatigue syndrome. Aoki T Miyakoshi H Usuda Y Herberman RB. Clinical Immunology and Immunopathology 1993 693 25365. Immunologic abnormalities associated with chronic fatigue syndrome. Barker E Fujimura SF Fadem MB Landay AL Levy JA. Clinical Infectious Diseases 1994 18Suppl 1 S13641. Description of poor mans tilt table testing procedure courtesy of Dr. Mary Schweitzer You lie still and rest for 15 minutes to 20 minutes. Then they take your</p>	

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		<p>blood pressure and pulse. Then you sit up for about 10 minutes same thing. Then you stand and lean slightly against a wall do NOT flex your muscles or struggle or talk. Be calm. Have somebody there who can catch you if there is trouble After ten minutes they should do the blood pressure and pulse again. Keep leaning. DO NOT FLEX ANY MUSCLES OR TALK. After another ten minutes take them again. If at any time you start to feel sweaty or hot or nauseous or basically super M.E. they need to do the bp and pulse right away and get you lying down. Congratulations. For Neurally Mediated Hypotension NMH you have to have a 20/25 mm drop in systolic blood pressure the higher number. If your pulse suddenly rises at least 30 bpm beats per minute then you have Postural Orthostatic Tachycardia Syndrome POTS. Dr. Rowe believes they are both really the same thing with either if you don't get down you're going to pass out. And the treatment for both is the same. Rowe published the first article on the relationship between CFS and autonomic nervous system dysfunction NMHPOTS in JAMA in the fall of 1995. Note See abstract below. What is neurally mediated hypotension Neurally mediated hypotension is also known by the following names the fainting reflex neurocardiogenic syncope vasodepressor syncope the vasovagal reflex and autonomic dysfunction. Hypotension is the formal medical term for low blood</p>	
Public Reviewer # 52	General	<p>As a patient with MECFS for eight years I am deeply concerned that the inclusion of the Oxford definition and acceptance of the PACE trial conclusions will destroy any attempts at finding real and effective treatments for MECFS. I am certain it will harm patients.</p>	<p>We have expanded on the limitations of the PACE trial and its applicability.</p>
Public Reviewer # 42	General	<p>The Executive summary is confused and does not clearly summarize the findings. For example in the body of the report the evaluation methods are clearly divided into 3 types Biomarkers Self reported symptom scales and Exercise testing. This is a simple and key point that should be present in the Executive Summary along with why they are still insufficient. The PACE trial has been the subject of complaint to the Lancet and the UK's Medical Research Council and is considered to be deeply flawed.</p>	<p>Thank you for your comments. We have made substantial changes to the executive summary to make it a more succinct document.</p>

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Public Reviewer # 15	General	<p>The studies that the reviewers included were not only too few they were completely inadequate to properly address the Key Questions. The Key Questions to be addressed by the report are as follows:</p> <ol style="list-style-type: none"> 1. What methods are available to clinicians to diagnose MECFS and how do the use of these methods vary by patient subgroups? 2. What are widely accepted diagnostic methods and what conditions are required to be ruled out or excluded before assigning a diagnosis of MECFS? 3. What is the accuracy and concordance of diagnostic methods? 4. What harms are associated with diagnosing MECFS? 5. What are the a) benefits and b) harms of therapeutic interventions for patients with MECFS and how do they vary by patient subgroups? 6. What are the characteristics of responders and nonresponders to interventions? <p>There are problems with the wording of some of these questions. For example in a country in which 80% of the physicians don't believe that CFS is a real disease what could widely accepted be referring to? And "What harms are associated with diagnosing MECFS" seems to have an a priori assumption that diagnosing the disease may in itself cause harm. But aside from the oddness of the wording the studies they chose do not adequately address the questions. The criteria for exclusion from the review included among others that the study did not last long enough (therapeutic trial of less than 12 weeks was published before 1988) had wrong study design or did not address a Key Question. There were 8 more exclusions. From among the thousands of studies that have been conducted the criteria limited the review to a scant 64 studies. Some of the landmark studies that were excluded were all of the studies demonstrating immune dysfunction e.g. NK cell deficiency studies by Brenu et al. studies of viral reactivation and antiviral treatments e.g. all Lerner and Jessop studies Kerr parvovirus B19 study studies documenting brain abnormalities e.g. Langes MRI study and all of the papers published by Tom Kindlon on harms associated with GET and CBT. Not even appearing on the excluded list were the groundbreaking 2-day CPET studies conducted by Keller Stevens and Snell Peckermans cardiac insufficiency studies and the recent Watanabe study on CNS inflammation. The fact that some of the most significant studies in the MECFS literature did not even appear on the excluded list was mindboggling. Of the studies that appeared on the exclusion list the reasons given were various but among the most frequently cited were that the studies did not address the Key Questions. Yet several studies that directly addressed the Key Questions were omitted for example 2-Day CPET studies were not even considered while studies that did not directly address the Key Questions were included. This arbitrariness permeated the entire study selection process. See more at http://pcfstreatment.blogspot.com/2014/09/theahrqdraftreportfundamentallyand.html and ash.tzk1XvLH.dpuf</p>	<p>Thank you for your comments. We have reworded the first question to improve readability without changing the content. Intermediate outcomes, including biomarker studies, were beyond the scope of this report.</p>

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Public Reviewer #57	General	I have been ill with ME for nearly 18 years following an infection with mononucleosis at age 24. For the first few years at doctors orders I forced myself to continue to work fulltime with extreme difficulty and also followed their mistaken directive of GET and CBT as treatments. As a result I had a massive setback that led me bedridden and I have remained so for nearly 14 years. I cannot stand walk fully bathe myself or speak more than a few words above a whisper. This is in large part due the the very treatments you describe as helpful. For more of my story please see my testimony to the CFS Advisory Committee which was presented in 2009 https://www.youtube.com/watch?v=VweCk44WHs . Since I am too ill to write a lengthy reply I am sharing Public Reviewer # 39s public commentary instead which I agree with completely. Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome MECFS Raise Questions of the Reviews Fitness for Purpose by Public Reviewer # 39 S.E. http://bit.ly/1r1XWBt Thank you.	Thank you for sharing your story.
Sister Sandra Duma	General	ME versus CFS/ME is NOT a subset of Chronic Fatigue Syndrome. ME existed long before CFS was invented by Fukuda and associates. ME is recognized by the World Health Organization who lists it as a neurological disease. The invention of CFS which watered down the disease ME which was subsequently further watered down through other variations under the CFS label continues to be a significant blunder and medical tragedy that has harmed patients and their families for decades. Patients harmed include those with ME as well as those with other illnesses mistakenly given the CFS label. CFS became a waste basket diagnosis. In many arenas it became a joke. CFS with its various definitions and emphasis on FATIGUE cause confusion and obliterate the true nature of ME. Yes patients given the CFS label were and continue to be stigmatized and traumatized. Chronic Fatigue Syndrome CFS needs to be done away with completely. Furthermore according to its definition CFS is medically unexplained fatigue lasting for 6 months or longer. Newsflash the fatigue ME or MECFS see note below patients experience is no longer medically unexplained. Current research is uncovering many physiological abnormalities including pathological dysregulation of the nervous immune and endocrine systems with impaired cellular energy metabolism and ion transport problems. Postexertional malaise or postexertional collapse as it is also called is a central feature of the disease ME. Clearly treatments for ME are not and should not be the same as treatments for depression and burnout. Cognitive behavioral therapy and graded exercise therapy may be able to help the latter but they are not any significant therapy for the former. If CFS is not completely done away with at the very least ME by the very definition of CFS as medically unexplained fatigue needs to be removed from that categorization. Note MECFS is often used by ME patients to distinguish themselves from CFS which can include anything from depression to burnout. It was an acronym adopted by some patients and some clinicians and researchers	Thank you for your comments. We have reworded the statement regarding the terms used to describe the condition. Review of etiology or pathophysiology of ME/CFS is beyond the scope of this review. We erred on being more inclusive with the case definitions since there is no agreed upon gold standard. We have pointed out the limitations and applicability of these varying case definitions. However, it was our job to lay out the state of the evidence as it exists today.

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		<p>to be used until such time as CFS could be dropped with the true name of the illness Myalgic Encephalomyelitis ME being used everywhere around the globe. The emphasis on fatigue for your literature review and the inclusion of the various CFS definitions was futile and worthless. It has no meaningful applications. It adds to the confusion surrounding this whole issue and further traumatizes ME patients who feel that the disease that has stolen their lives will once again be made to disappear. We wonder why the original search questions were changed. We wonder why given the serious and complicated nature of ME ME experts who have worked with this illness up close for years were not given the charge to lead these projects. We wonder if this whole thing was orchestrated from the beginning to get the results the NIH wanted instead of a true research effort. The question remains Will the IOM and P2P projects truly help those afflicted with ME by setting the whole story straight about this disease or will ME once more be made to disappear in confusion and obliteration Patients have waited for 30 years for our disease ME to be taken seriously. We wonder if projects such as this P2P effort will set us back another 30 years. Sister Sandra Duma Submitted October 7 2014</p>	
Public Reviewer # 16	General	<p>I am writing to request the cancellation of the P2P Workshop on MECFS. I believe that the P2P Workshop will not advance us towards the much needed MECFS research case definition or strategy for the following reasons MECFS experts have already adopted the Canadian Case Definition for research. No new definition is needed. The Workshop is examining the wrong illness. They are examining medically unexplained fatigue not MECFS. NIH has not engaged or involved stakeholders in a substantive way. The Workshop panel consists of nonMECFS experts. HHS has made numerous contradictory statements about the purpose of the Workshop so its goal is unclear. The recent draft report from AHRQ is inaccurate selfcontradictory and reflects a poor understanding of MECFS research. The panel notes that the Oxford definition could include patients without MECFS but includes those patients in their review anyway. The review included nine treatment studies based on the Oxford definition. The review rated the PACE trial and two other Oxford CBTGET counseling studies as good. Careful consideration of the above issues raises legitimate concerns about whether the P2P Workshop will produce good science and sound recommendations. I hope you will give my concerns a fair hearing and that you will cancel the P2P Workshop.</p>	<p>The organization and process of the P2P workshop is beyond the scope of this review and outside of our jurisdiction. We erred on the side of being more inclusive with the case definitions as there is no agreed upon gold standard. We have expanded our results section and highlighted the case definitions for inclusion as well as the limitations associated with this.</p>
Bianca Lindstrom	General	I fully support and endorse the comments sent in earlier by Public Reviewer # 39.	Thank you - noted.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #17	General	<p>Comments regarding the AHRQ review for MECFS No specificity as to what illness is being studied it appears many Medically fatiguing illnesses were lumped in the same category as MECFS. MECFS is a complex misunderstood illness. For the panel to be comprised of nonexperts reviewing studies and making determinations regarding diagnosis and treatment that know nothing about MECFS is absolutely ridiculous. Misinterpretation of cited literature. If the panel consists of persons with no prior knowledge of a complicated illness and some literature reviews included persons with fatigue and not MECFS... plus have no understanding of the definitions used for inclusion and exclusion critia how can any recommendations be sound Recent biological findings published in the literature including those demonstrating the harms done with exercise to MECFS patients were not included. However the Pace trial with all its flaws and problems were included and obviously misinterpreted. Medical Experts in MECFS have already adopted the Canadian Consensus Criteria for research and clinical purposes. This entire P2P workshop is a waste of time and tax payers dollars and should be cancelled. Thank you for your attention to these critical concerns that affect all the patients debilitated by this illness their families and health care providers.</p>	<p>Thank you for your comments. We engaged experts in the field as well as patients when developing the scope and key questions. We included a consultant physician who has spent years treating people with ME and CFS on our review team to help inform the review. We have expanded our discussion and highlighted the limitations of studies, including the PACE trial.</p>

Commentator & Affiliation	Section	Comment	Response
Charmian Proskauer	General	<p>Re Abstract Reading just the abstract of the Draft Comparative Effectiveness Review for Diagnosis and Treatment of Myalgic Encephalomyelitis Chronic Fatigue Syndrome MECFS as busy clinicians and lay people will do gives the clear impression that aside from one drug that turns out not to be available in the U.S. CBT and GET are the only proven interventions that improve outcomes for patients at least with some benefit although GET may be associated with significant harms. So presenting a behavioral intervention as the only evidencebased treatment clearly reinforces the widelyheld impression that MECFS is a psychological illness which MECFS researchers clinicians and patients know to be false. This comment is an addendum to my previous comment and suggests an answer to the question I asked. As stated in my previous comment SO given that this section is likely to be the ONLY part read by ordinary doctors and the general public and reported on by the press is there some way to rewrite it to provide a broader context for the evidence that does not reinforce the stereotypes that patients have been struggling against for YEARS sentence such as the following might work. Although it probably does not fit with the template used for these reports it might be justified in this case in order to avoid significant harm to patients which will happen if it is left out. Limitations. Diagnostic tests were not well studied in a broad spectrum of patients. Intervention studies were scarce and most were either fair or poor quality and measured outcomes using heterogeneous methods making it difficult to compare results across studies. Add to Limitations section Due to the limited scope of this Review studies on diagnosis and treatments only and the very strict application of inclusionexclusion criteria many studies showing etiology or pathophysiology of this condition were not included. Also because of the limited range of treatment studies which were included and reviewed no conclusions should be drawn from this report about the nature of the illness or other possible treatments which could help patients more than those cited here.</p>	<p>Thank you for your comments. We have expanded our discussion and highlighted the limitations of studies with an emphasis on consideration of the case definition used for inclusion. Discussion of etiology, pathophysiology, or theories surrounding why one treatment may be effective or not, is beyond the scope of this review.</p>
Public Reviewer #61	General	<p>In regard to the Research Review Draft Sept. 22 2014 Diagnosis and Treatment of Myalgic Encephalomyelitis Chronic Fatigue Syndrome MECFSAs a 25 year sufferer of M.E. and founder of the Springfield Ohio MEFMCFSGWI support group I have closely followed the studies on M.E. CFS Fibromyalgia and Gulf War illness. I have also followed the government response and have been dismayed that the science is repeatedly ignored and underfunded. From this report The information in this report is intended to help health care decision makers patients and clinicians health system leaders and policymakers among othersmake well informed decisions and thereby improve the quality of health care services. If this statement is true then a full rework of the proposal is required. The definition of insanity is doing the same thing over and over and expecting a different result. And yet this report repeats the mistakes of the past. Specifically This report neglected to include a number of studies and scientific discoveries which are at</p>	<p>Thank you for sharing your story. We erred on the side of being more inclusive with the case definitions. If we were to only include studies of patients with PEM, there would have been much less to help inform the current understanding of the syndrome of ME/CFS. Of note, we did not consider intermediate outcomes including biomarkers or studies addressing etiology/pathophysiology.</p>

Commentator & Affiliation	Section	Comment	Response
		<p>the core of the illness. Due to lack of funding for larger studies the targeted studies done in this field have been small scale. The decision to ignore these smaller scale studies is at the heart of the mistake made in this report. The studies used to create this report have been done on a broad definition of CFS which means they are NOT studies which apply to M.E. sufferers as defined by the International Consensus Criteria nor the Canadian Consensus Criteria which are the accepted criteria of the experts in the field. Any study included in any report about Myalgic Encephalomyelitis must include only patients with the symptom of Post Exertion Malaise PEM since PEM is a required symptom for anyone diagnosed with M.E. Here are two examples of reports which should have been included Yasuhito Nakatomi Kei Mizuno Akira Ishii Yasuhiro Wada Masaaki Tanaka Shusaku Tazawa Kayo Onoe Sanae Fukuda Joji Kawabe Kazuhiro Takahashi Yosky Kataoka Susumu Shiomi Kouzi Yamaguti Masaaki Inaba Hirohiko Kuratsune Yasuyoshi Watanabe Neuroinflammation in patients with chronic fatigue syndromemyalgic encephalomyelitis a 11CRPK11195 positron emission tomography study The Journal of Nuclear Medicine vol.55 No.6 2014 DOI 10.2967/jnumed.113.131045 Christopher R. Snell Staci R. Stevens Todd E. Davenport and J. Mark VanNess. 2013. Discriminative Validity of Metabolic and Workload Measurements to Identify Individuals with Chronic Fatigue Syndrome. PHYS THER. Published online June 27 2013 doi 10.2522/ptj.20110368 By including those studies a much more accurate report would have been made. A study which should never have been included is the flawed PACE trial. This was bad science and has led to harmful treatments for many sufferers including death by over exertion and suicide from exacerbation of symptoms. Lumping M.E. sufferers with CFS sufferers and using the names interchangeably indicates the writers of the report have not done their homework. If the preparers of this report had used the more reliable studies it would have been clear to them how CFS and M.E. are differentiated and using the names interchangeably would not have been considered. This report instead of making the situation for sufferers better is expected to have the opposite effect.</p>	
Public Reviewer # 43	General	<p>I have more concerns with the exclusion of some good research and overemphasis on the inaccurate falsified results reported in the PACE trials but my current level of brain fog and inability to communicate my thought processes precludes me from going into more detail. I appreciate the work that you have put into this process and remain hopeful that you will use the patient advocacy input to come to a true definition of this dreadful disease. Thirty three years is a long time to wait for a credible name and definition of this disease that has stolen my life and health.</p>	<p>Thank you for sharing your story. We have expanded our discussion of the limitations of studies including the PACE trial.</p>
Public Reviewer # 18	General	<p>To whom it may concern Most fundamentally the Evidence Review is grounded in the flawed assumption that eight CFS and ME definitions all represent the same group of patients that are appropriately studied and treated as a single entity or</p>	<p>We erred on the side of being more inclusive with the case definitions since there is no gold standard. We have</p>

Commentator & Affiliation	Section	Comment	Response
		<p>group of closely related entities. Guided by that assumption this Evidence Review draws conclusions on subgroups diagnostics treatments and harms for all CFS and ME patients based on studies done in any of these eight definitions. In doing so the Evidence Review disregards its own concerns as well as the substantial body of evidence that these definitions do not all represent the same disease and that the ME definitions are associated with distinguishing biological pathologies. It is unscientific illogical and risky to lump disparate patients together without regard to substantive differences in their underlying conditions. Compounding this flawed assumption are the a priori choices in the Review Protocol that focused on a more narrow set of questions than originally planned and that applied restrictive inclusion and exclusion criteria. As a result evidence that would have refuted the flawed starting assumption or that was required to accurately answer the questions was never considered. Some examples of how these assumptions and protocol choices negatively impacted this Evidence Review include Evidence about the significant differences in patient populations and in the unreliability and inaccuracy of some of these definitions was ignored and/or dismissed. This includes Dr. Leonard Jason's work undermining the Reeves Empirical definition a study that shows the instability of the Fukuda definition over time in the same patients studies demonstrating that Fukuda and Reeves encompass different populations and differences in inclusion and exclusion criteria especially regarding PEM and psychological disorders. Diagnostic methods were assessed without first establishing a valid reference standard. Since there is no gold reference standard each definition was allowed to stand as its own reference standard without demonstrating it was a valid reference. Critical biomarker and cardiopulmonary studies some of which are in clinical use today were ignored because they were judged to be intended to address etiology regardless of the importance of the data. This included most of Dr. Snells and Dr. Kellers work on two day CPET Dr. Cooks functional imaging studies Dr. Gordon Brodericks systems networking studies Dr. Klimass and Dr. Fletchers work on NK cells and immune function and all of the autonomic tests. None of it was considered. Treatment outcomes associated with all symptoms except fatigue were disregarded potentially resulting in a slanted view of treatment effectiveness and harm. This decision excluded Dr. Lerner's antiviral work as well as entire classes of pain medications antidepressants antiinflammatories immune modulators sleep treatments and more. If the treatment study looked at changes in objective measures like cardiac function or viral titers it was excluded. If the treatment study looked at outcomes for a symptom other than fatigue it was excluded. Treatment trials that were shorter than 12 weeks were excluded even if the treatment duration was therapeutically appropriate. The big exclusion here was the rituximab trial despite following patients for 12 months it was excluded because administration of rituximab was not continuous for 12 weeks even</p>	<p>highlighted the differences between case definitions and expanded our discussion of this in the limitations section. We have discussed the limitations in diagnosis when there is a lack of a reference standard and have used standard methodology to address this limitation. Biomarker and cardiopulmonary studies as addressing diagnosis were included in the report if they met the inclusion criteria. Cardiopulmonary testing was included if used as a measure of function in a clinical trial but other intermediate outcomes including biomarker studies, imaging were not included for this review.</p> <p>The Key Questions and scope were based on what can be accomplished by a systematic review process. Other speakers and experts will address the other areas of the P2P conference that cannot be covered by the evidence review.</p>

Commentator & Affiliation	Section	Comment	Response
		<p>though rituximab is not approved for 12 weeks continuous administration in ANY disease. Many other medication trials were also excluded for not meeting the 12 week mark. Counseling and CBT treatment trials were inappropriately pooled without regard for the vast differences in therapeutic intent across these trials. This meant that CBT treatments aimed at correcting false illness beliefs were lumped together with pacing and supportive counseling studies and treated as equivalent. Conclusions about treatment effects and harms failed to consider what is known about ME and its likely response to the therapies being recommended. This means that the PACE an Oxford study results for CBT and GET were not only accepted despite the many flaws in those data but were determined to be broadly applicable to people meeting any of the case definitions. Data on the abnormal physiological response to exercise in ME patients were excluded and so the Review did not conclude that CBT and GET could be harmful to these patients although it did allow it might be possible. The Evidence Review states that its findings are applicable to all patients meeting any CFS or ME definition regardless of the case definition used in a particular study. The issues with this Evidence Review are substantial in number magnitude and extent. At its root is the assumption that any case definition is as good as the rest and that studies done on one patient population are applicable to every other patient population despite the significant and objective differences among these patients. The failure to differentiate between patients with the symptom of subjective unexplained fatigue on the one hand and objective immunological neurological and metabolic dysfunction on the other calls into question the entire Evidence Review and all conclusions made about diagnostic methods the nature of this disease and its subgroups the benefits and harms of treatment and the future directions for research. As the Evidence Review states the final version of this report may be used in the development of clinical practice guidelines or as a basis for reimbursement and coverage policies. It will also be used in the P2P Workshop and in driving NIHs research strategy. Given the likelihood of those uses and the Evidence Reviews claim of broad applicability to all CFS and ME patients the flaws within this report create an undue risk of significant harm to patients with ME and will likely confound research for years to come. These issues must be addressed before this Evidence Review is issued in its final form. Toby Vokal ME patient 19 years</p>	

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #62	General	I am writing to protest the entire P2P process including the production of this report. I have had ME for 24 years and am outraged at the US Department of Health Human Services HHS pretense that P2P is responsive to the Chronic Fatigue Syndrome Advisory Committee CFSAC October 2012 recommendation to convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition useful for research diagnosis and treatment. In no way is the P2P process responsive to this recommendation. NIH has not engaged or involved stakeholders in a substantive way. The Workshop panel consists of individuals with no expertise in ME or CFS. It ignores the subsequent letter to HHS by disease experts who have adopted the Canadian Case Definition for research to be updated as needed. Instead the focus of the draft report is medically unexplained fatigue. By using evidence-based practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possibly worse than what has already been inflicted on people like me. For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purposes.	Thank you for sharing your story. The organization of the P2P workshop and process is beyond the scope of this report.
Public Reviewer # 19	General	I protest the entire P2P process including the publication of this report its dissemination to the P2P panel and anything that follows. I will not participate in any attempt by HHS to continue to harm ME patients.	Thank you - noted.
Public Reviewer #63	General	To Scientific Resource Center Portland VA Research Foundation Subject Comments on the AHRQ Evidence Review Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Date October 18 2014 Myself and others share the same concerns in Canada and request the same diligence in sorting out the questions posed in the document above. We have been sick and disabled for many years and this pre-report does not seem to be helping our position for increased biological research funding proper understanding by physicians and medical staff or treatment options. We have done this grueling journey for years. This is not helping. Please address and correct these concerns before going further. Thank you Valerie Free patient and author of this illness story to be released next year. Randy Warner patient who is bedbound primarily Lisa Wolfe patient who is moderately severe and unable to work and function with any ease. There are thousands of Canadians who will be influenced by this decision along with many other countries. Everyone is watching and waiting for appropriate care treatment and funding to correct a historical calamity of suffering. This is a beginning to change our lives and it needs to be done differently.	Thank you - noted.

Commentator & Affiliation	Section	Comment	Response
Emily Craven	General	<p>As the goal of the P2P program is to identify research gaps in a selected scientific area identify methodological and scientific weaknesses in that scientific area it is essential that the P2P program be aware of the existing research. However the AHRQ Reports strident and narrow criteria excluded an estimated 90 of the literature on MECFS. Among this excluded research are groundbreaking biological findings MECFS patients inability to replicate work levels on 2day CPET low NK cell function and more that could be evaluated for diagnostic criteria. Some of this research was done with NIH grants Fletcher. Inclusion of the highly controversial PACE trial and focus on CBT and GET as treatments is disconcerting. As is the lack of distinction in the report between CBT as an intervention to assist patients in coping with an organic chronic illness and CBT as an intervention to correct aberrant illness beliefs. Noting the negative effects of being given a MECFS diagnosis while failing to discuss the benefits is highly problematic. The implication would seem to be a concern that diagnosis fuels something akin to hypochondriasis rather than an organic illness that exists regardless of diagnosis in which case a diagnosis may be helpful. For instance staying within ones energy envelope pacing and not overexerting oneself are crucial to the patients prognosis. Once a patient is diagnosed they can begin to implement these lifestyle changers whereas without a diagnosis they have no way to know that pushing themselves beyond their limits may cause lasting damage as was my experience. Although I support the reports claims that current research is insufficient and studies need more participants I am concerned about the way existing research was represented. Specifically I am concerned that the authors may have erred on the side of popular bias in misunderstanding the severity seriousness and organic nature of this illness.</p>	<p>Thank you for your comments. Cardiopulmonary testing was included if used as a measure of function in a clinical trial, but other intermediate outcomes, including biomarker studies and imaging were not included for this review. Discussion of the etiology/pathophysiology of ME/CFS as well as the theories surrounding why one treatment may work or not is beyond the scope of this report. We have expanded our discussion of the limitations of the evidence and performed a repeat analysis looking strictly at the CBT studies rather than including them with other forms of counseling or behavioral therapy.</p>
Public Reviewer # 20	General	<p>I believe the P2P study fundamentally flawed for not accepting the scientific 2 day CPET trial which clearly showed PENE this cannot be faked.It is what every ME sufferer will live with day to day hour to hour.It clearly shows a biomarker for an underlying disease process.Also ignoring the Rituximab trials is astonishing also taking evidence from only the 1980s is ridiculous omitting the research from the royal free outbreak where the study from this outbreak showed that those who fought the disease physically became the more severely disabled.The PACE trials considerable flaws are not looked at aswell as those deemed to be recovered were still severely disabled aswell as recovered points scale was lowered whilst the trial was ongoing.I was made permanently severely disabled for life because of not resting in the early years.My illness can be measured scientifically anytime by CPET.The ICC ME states that the body MUST adapt its behaviour to avoid further damage.Your study as it stands will harm patients.Also my mitochondria when measured shows damage scientifically.</p>	<p>Thank you for your comments. We a priori elected to not include intermediate outcomes. We also did not include diagnosing specific symptoms of ME/CFS, including PEM, which is addressed in the 2-day CPET trial. We have expanded our discussion of the limitations of the trials, including the PACE trial.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #64	General	Nonexperts your draft leaves us aghast. Your report as it stands with your acceptance of the Oxford definition and the PACE trial which you rate good will harm us us desperately ill patients already beaten down by the years decades of NIH indifference.	Thank you for your comments. One role of this review is to highlight areas for future research. We have described the limitations of the current trials and have expanded our discussion of future research needs.
Public Reviewer # 46	General	Hi I am a registered nurse who worked fulltime maintained a clean home raised a family and exercised regularly throughout my life until I got the flu December 24 2009. Up until that time I described myself as a person who never sat down The week I got the flu I was still riding a bike 200 miles a week and in fact my vacation was a 550 mile road bike ride over three mountain passes through the state of Washington in one week. I lived to snow ski in the winter and kayak raft and swim in the summer along with scuba diving in. I gave birth to my three children at home with no drugs and certainly was not a wimp when it came to taking pain I had never heard of chronic fatigue syndrome or post viral syndrome and as a registered nurse I fear things like AIDS or hepatitis I must confess when I learned about fibromyalgia in the 1980s that I had an attitude of arrogance and thought that those people would all be a lot better off if they exercised like me. I also bought into all the media about a bunch of yuppies in New York malingering and claiming to have some type of fatiguing illness I now lie here a very humbled woman at the mercy of myalgic encephalomyelitisnot chronic fatigue syndrome Fatigue is one of many symptoms of myalgic encephalomyelitis but I have ridden a bicycle 550 miles in a week and never felt like this It is like the worst day of the worst flu youve ever had only it never goes away The pain is on unimaginable and during the first two years I fought the logic of committing suicide daily not because I wanted to be dead but because I wanted to be released from the torture of living in my body and the hopelessness of waking up every day still so desperately sick I am sentenced to lie in bed in isolation and that is the worst part of it all after all this is how very very bad people are punished in prison they sit alone in rooms day after day with no hope. My legs felt like tree trunks too heavy to lift when I tried to lift them to walk and even a cup of juice felt heavy to lift. I waited to void until it hurt and then crawled to get to the bathroom. I would go without food at times because I couldnt get it for myself. At times and I had help I was even too weak to lift the spoon to my mouth. My appetite abruptly changed and all I could eat was oranges salads and milk during the first year. I had developed a strange new aversion to any type of meat or alcoholwhich I barely drank prior to getting ill but now even a commercial about it brought on nausea. I could not comprehend anything I read at times and I could barely comprehend television programs when I was able to tolerate the noise from them. I would have to rewind the TV repeatedly in order to understand the program. Paying my bills took days because I would get so confusedand had trouble calculating. I had to	Thank you for sharing your story.

Commentator & Affiliation	Section	Comment	Response
		<p>make a list to remember what to do to get ready for bed brush my teeth wash my face and so on. I would take a bath and literally sit on the floor too short of breath and weak to get dressed for an hour. I finally started having an hour or two where I felt better apnd could be up and thought that maybe I was getting well. I even tried to exercise but found that it caused me to crash and I would be back in bed for days or weeks again. I constantly suffered with a sore throat a very weak hoarse voice and tender glands in my neck for the first four years now they come and go and generally signal a crash coming on. I am bed or couch bound approximately 80 of the year now as opposed to 100 when I first got sick. I never feel normal but able to get up and do some light housework and prepare my own food and even get out to the grocery store at times. This is not living this is staying alive</p>	
Patient25	General	<p>I am writing to protest the entire P2P process including the production of this report. I have had ME for 25 years and am outraged at the US Department of Health Human Services HHS pretense that P2P is responsive to the Chronic Fatigue Syndrome Advisory Committee CFSAC October 2012 recommendation to convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition useful for research diagnosis and treatment. In no way is the P2P process responsive to this recommendation. NIH has not engaged or involved stakeholders in a substantive way. The Workshop panel consists of individuals with no expertise in ME. It ignores the subsequent letter to HHS by disease experts who have adopted the Canadian Case Definition for research to be updated as needed. Instead the focus of the draft report is medically unexplained fatigue. By using evidencebased practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possible worse than what has already been inflicted on people like me. For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purposes.</p>	<p>Thank you for sharing your story. The organization of the P2P workshop and process is beyond the scope of this report. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded on this in the discussion section.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 39	General	I am writing to protest the entire P2P process including the production of this report. As a structural engineer who had my career and active life taken away by the neurological disease myalgic encephalomyelitis ME 17 years ago I am outraged at the US Department of Health and Human Services HHS pretense that P2P is responsive to the Chronic Fatigue Syndrome Advisory Committee CFSAC October 2012 recommendation to convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition useful for research diagnosis and treatment. In no way is the P2P process responsive to this recommendation. NIH has not engaged or involved stakeholders in a substantive way. The Workshop panel consists of individuals with no expertise in ME or CFS. It ignores the subsequent letter to HHS by disease experts who have adopted the Canadian Case Definition for research to be updated as needed. Instead the focus of the draft report is medically unexplained fatigue. By using evidencebased practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possible worse than what has already been inflicted on people like me. For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purposes.	Thank you for sharing your story. The organization of the P2P workshop and process is beyond the scope of this report. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded on this in the discussion section of the report.
Public Reviewer # 47RN ACRN	General	I am writing to protest the P2P process being used to evaluate Diagnosis and treatment of MECFS. Patients with MECFS have been told by our government that P2P is part of the official response to the October 2012 CFSAC recommendation to convene a stakeholder workshop including experts patients and advocates to achieve consensus for a case definition working from the 2003 Canadian Consensus Criteria. I cannot overstate my personal and professional opposition to this process. As a patient living with this disease for 30 years and a Registered Nurse involved in NIH sponsored HIV/AIDS research for 20 years I am appalled that HHS believes P2P is an appropriate response to the CFSAC recommendation. The Workshop panel consists of individuals with no expertise in ME or CFS. P2P ignores a letter to HHS by recognized MECFS experts recommending the Canadian Case Definition. The AHRQ draft report contains numerous factual and conceptual errors. It depends on a biased sample of research studies. Many valid studies published in nonindexed journals were excluded from the review. Studies from psychological literature are overrepresented in the Review. Lastly there has been no true effort to engage stakeholders especially patients and advocates. For these and many other reasons I object to the continuance of the P2P process including publication of the AHRQ Draft report its dissemination to the P2P panel and its use for any other future purposes.	Thank you for sharing your story. The organization of the P2P workshop and process is beyond the scope of this report. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded on this in the discussion section.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #65	General	Having suffered with MECFS for 14 years and unable to work for the past 4 I must voice my concerns over having a nonexpert panel let alone one reviewing literature that is less than specifically applicable to this condition. Accept the Canadian definition as is or adopt it and refine it as new information develops. Having pursued a wide variety remedies and undertaken many tests including the 2 day CPET I can attest with complete certainty that CBT is of no help and GET worsens my condition. I and millions of Americans and people globally remain incapacitated as the years roll by. There is no need to reinvent the wheel. There is great need to act with urgency and get the research going.	Thank you for sharing your story. We have followed sound methodology for conducting systematic reviews. Additionally, we included patients and experts on our Technical Expert Panel and throughout the review process had on our team a consultant who is an expert in ME/CFS.
Public Reviewer #66	General	P2P will harm patients I am writing to protest the entire P2P process including the production of this report. I have had ME for 39 years and my daughters since birth. Since 5 re 4 years they are both very severely affected bedridden and spoonfed. I am outraged at the US Department of Health Human Services HHS pretense that P2P is responsive to the Chronic Fatigue Syndrome Advisory Committee CFSAC October 2012 recommendation to convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition useful for research diagnosis and treatment. In no way is the P2P process responsive to this recommendation. NIH has not engaged or involved stakeholders in a substantive way. The Workshop panel consists of individuals with no expertise in ME or CFS. It ignores the subsequent letter to HHS by disease experts who have adopted the Canadian Case Definition for research to be updated as needed. Instead the focus of the draft report is medically unexplained fatigue. By using evidencebased practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possible worse than what has already been inflicted on people like me. For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purposes.	Thank you for sharing your story. The organization of the P2P workshop and process is beyond the scope of this report. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded on this in the discussion section of the report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 21	General	I am writing to PROTEST the ENTIRE P2P process including the production of the report. I had had M.E. for over 26 YEARS and am OUTRAGED at the US Dept. of Health Human Services HHS pretense that P2P is responsive to the Chronic Fatigue Advisory Committee CFSAC Oct. 2012 recommendation to convene a Stakeholder Workshop including experts patients and advocates to reach a consensus for a case definition useful for research diagnosis and treatment. In NO WAY is the P2P process responsive to this recommendation. NIH has NOT engaged or involved Stakeholders in a substansive way. The workshop panel consists of individuals with NO EXPERTISE in M.E. or CFS. It IGNORES the subsequent letter to HHS by disease EXPERTS who have ADOPTED the Canadian Consensus definition for research to be updated as needed. Instead the focus of the draft report is Medically unexplained fatigue By using evidencebased practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possibly worse than what has already been inflicted on people like me For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purpose. signed a very angry M.E. Patient	Thank you for sharing your story. The organization of the P2P workshop and process is beyond the scope of this report. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded on this in the discussion section of the report.
Public Reviewer # 22	General	I am writing to protest the entire P2P process including the production of this report. I have had ME for 15 years and am outraged at the US Department of Health Human Services HHS pretense that P2P is responsive to the Chronic Fatigue Syndrome Advisory Committee CFSAC October 2012 recommendation to convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition useful for research diagnosis and treatment. In no way is the P2P process responsive to this recommendation. NIH has not engaged or involved stakeholders in a substantive way. The Workshop panel consists of individuals with no expertise in ME or CFS. It ignores the subsequent letter to HHS by disease experts who have adopted the Canadian Case Definition for research to be updated as needed. Instead the focus of the draft report is medically unexplained fatigue. By using evidencebased practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possible worse than what has already been inflicted on people like me. For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purposes.	Thank you for sharing your story. The organization of the P2P workshop and process is beyond the scope of this report. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded on this in the discussion section.

Commentator & Affiliation	Section	Comment	Response
Penelope McMillan	General	I am very concerned that a panel composed largely of people who are neither experts nor stakeholders is claiming to be undertaking a process that requires expert knowledge and understanding. In particular I am concerned that due to ignorance of the research issues surrounding this group of illnesses fraudulent and misleading research results are being favoured over rigorous smaller studies. This panel process is necessarily flawed and should be discontinued.	Thank you for sharing your story. We have followed sound methodology for conducting systematic reviews. Additionally, we included patients and experts on our Technical Expert Panel and throughout the review process had on our team a consultant who is an expert in ME/CFS.
Public Reviewer # 23	General	I am writing to protest the entire P2P process including the production of this report. I have had ME for 18 years bedridden for over a decade and am outraged at the US Department of Health Human Services HHS pretense that P2P is responsive to the Chronic Fatigue Syndrome Advisory Committee CFSAC October 2012 recommendation to convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition useful for research diagnosis and treatment. In no way is the P2P process responsive to this recommendation. NIH has not engaged or involved stakeholders in a substantive way. The Workshop panel consists of individuals with no expertise in ME or CFS. It ignores the subsequent letter to HHS by disease experts who have adopted the Canadian Case Definition for research to be updated as needed. Instead the focus of the draft report is medically unexplained fatigue. By using evidence-based practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possibly worse than what has already been inflicted on people like me. For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purposes.	Thank you for sharing your story. The organization of the P2P workshop and process is beyond the scope of this report. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded this discussion.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 24	General	<p>I wish to strongly protest at the absurd way the set up of P2P where non experts are to decide on a complex disease to give advice. To limit only selected studies is absurd as well especially excluding the 2 day CPET by Professor Snell where the cardio science was proof of underlying pathophysiological abnormalities this cannot be disputed. I am now permanently severely disabled due to the fact that I tried to beat this disease in the early years working whilst ill in between successive relapses. How can you make clinical judgement when ignoring Dr Ramsay's definitive guide to ME who closely followed the outbreak of ME at the Royal Free Hospital he stated unequivocally that the level of disability was in direct correlation to the effort made to beat the disease those that rested had a more favourable longterm outcome. So Ramsay is to be ignored by the P2P because it is many years earlier than the dates you set did cancer start in 1980. The studies from the 1980s are all overwhelmingly biopsychosocial which are just no longer credible. Therefore your outcome will harm patients we have the knowledge and expertise already in The ICC CCC ME the salient clinical feature which can be objectively measured is Post Exertional Neuroimmune Exhaustion my level of symptoms is in direct correlation to effort made physical mental. Psychology plays no part in the actual illness itself as revealed by Professor Snell's studies. It should also be noted that the outgoing head of NICE was accepting to the ME Association verdict on the NHS Guidelines for ME that they are Unfit for purpose and stated change is needed especially on guidance re CBT GET it is NOT treatment. I am a member of the 25 Severe ME Group where a large number are now permanently severely disabled due to the ignorance of medical professionals due to bad advice instigated by powerful psychiatrists who dominate much of the absurd psychobabble written on ME. By the looks of what you have already released you will harm patients. The Norwegian Government has also apologised to patients following the success of the cancer drug Rituximab on severely affected patients.</p>	<p>Thank you for sharing your story. The organization of the P2P workshop and process is beyond the scope of this report. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded that discussion. We have followed sound methodology for conducting systematic reviews. Additionally, we included patients and experts on our Technical Expert Panel and throughout the review process had on our team a consultant who is an expert in ME/CFS.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #67	General	I am writing to protest the entire P2P process including the production of this report. I have had ME and Lyme Disease for 17 years and am outraged at the US Department of Health Human Services HHS pretense that P2P is responsive to the Chronic Fatigue Syndrome Advisory Committee CFSAC October 2012 recommendation to convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition useful for research diagnosis and treatment. In no way is the P2P process responsive to this recommendation. NIH has not engaged or involved stakeholders in a substantive way. The Workshop panel consists of individuals with no expertise in ME or CFS. It ignores the subsequent letter to HHS by disease experts who have adopted the Canadian Case Definition for research to be updated as needed. Instead the focus of the draft report is medically unexplained fatigue. By using evidencebased practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possible worse than what has already been inflicted on people like me. For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purposes. Please help us correct this. M.E. has a valid WHO code 93.3 USE IT	Thank you for sharing your story. The organization of the P2P workshop and process is beyond the scope of this report. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded this discussion.
Long term severe ME sufferer	General	I am writing to protest the entire P2P process including the production of this report. I have had ME for 20 years and am outraged at the US Department of Health Human Services HHS pretense that P2P is responsive to the Chronic Fatigue Syndrome Advisory Committee CFSAC October 2012 recommendation to convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition useful for research diagnosis and treatment. In no way is the P2P process responsive to this recommendation. NIH has not engaged or involved stakeholders in a substantive way. The Workshop panel consists of individuals with no expertise in ME or CFS. It ignores the subsequent letter to HHS by disease experts who have adopted the Canadian Case Definition for research to be updated as needed. Instead the focus of the draft report is medically unexplained fatigue. By using evidencebased practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possible worse than what has already been inflicted on people like me. For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purposes.	Thank you for sharing your story. The organization of the P2P workshop and process is beyond the scope of this report. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded this discussion.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #68	General	<p>Here is the central question Is MECFS an illness in which patients merely feel tired or is it an illness of physiologic impairment of energy As a patient and a medical historian I would argue the latter. However even allowing that either view could be true one must concede that they are two different problems requiring two different approaches for research and treatment. This evidence review does not acknowledge any such distinction. It does not even acknowledge the difference between the subjective study of fatigue through surveys and its objective study through physiologic mechanism. Rather it combines and compares the two like apples and oranges. The authors note that the report is in alignment with prior evidence reports indeed it is. Like prior reports this one fails to address what kind of fatigue it is examining. Perhaps that is one reason why MECFS research is in the muddled state it is. Fortunately biomedical science is already studying fatigue objectively through its research into mitochondrial dysfunction. Research in oncology already links fatigue in cancer and cancer treatment to malfunctioning mitochondria other work also ties fatigue in multiple sclerosis to such dysfunction. There is even research correlating mitochondrial dysfunction to fatigue in MECFS for reasons unclear this has been excluded from the evidence review. Why cant MECFS research take advantage of what oncology neurology and other fields already know Must it be continually consigned to a biologyfree zone</p>	<p>Thank you for your comments. We have reworded our first question to improve readability without changing the content and including only patients whereby ME/CFS is a diagnostic consideration. We have expanded our discussion of the differences between case definitions and how this impacts the selection of patients included in trials. Discussion of intermediate outcomes including biomarker studies as well as other studies of etiology are beyond the scope of this report.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 25	General	<p>I am writing to protest the entire P2P process including the production of this report. I have had ME without even the benefit of a clear diagnosis let alone treatment or support options since at least 1989 when hospitalized for ten days with severe viral and other unexplained illness from which I never recovered. I might add that I was later exposed to HIV 1997 Feb occasion known and I can assure you that the level of debility and functional impairment as well as the stigma have been far worse resulting from the unrecognized ME with which I have been left alone to manage for at least 27 years. I am also a licensed health care professional and am quite able to tell when I am physically ill. I am outraged at the US Department of Health Human Services HHS pretense that P2P is responsive to the Chronic Fatigue Syndrome Advisory Committee CFSAC October 2012 recommendation to convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition useful for research diagnosis and treatment. In no way is the P2P process responsive to this recommendation. NIH has not engaged or involved stakeholders in a substantive way. The Workshop panel consists of individuals with no expertise in ME or CFS. It ignores the subsequent letter to HHS by disease experts who have adopted the Canadian Case Definition for research to be updated as needed. Instead the focus of the draft report is medically unexplained fatigue. By using evidencebased practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possibly worse than what has already been inflicted on people like me. For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purposes.</p>	<p>Thank you for sharing your story. The organization of the P2P workshop and process is beyond the scope of this report. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded this discussion.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 26	General	<p>I am writing solely to protest the entire P2P process including the production of this report. It is an absolute outrage to claim that the US Department of Health Human Services HHS NIHs P2P is in any way responsive to the Chronic Fatigue Syndrome Advisory Committee CFSAC October 2012 unanimous recommendation to convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition useful for research diagnosis and treatment. IN NO WAY is the P2P process responsive to this recommendation. NIH has not engaged or involved stakeholders in any substantive way. The Workshop panel consists of individuals with no expertise in Myalgic Encephalomyelitis ME or CFS. The process also blatantly ignores the subsequent letter to HHS by disease experts who have adopted the Canadian Case Definition CCC 2003 for research to be updated as needed. Instead the focus of the draft report is medically unexplained fatigue. By using evidencebased practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possibly even worse than what has already been inflicted on people like me. For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purposes. You must cease this antiscientific shambolic affront to desperately needed progress for extremely ill people who deserve real research real treatment real help. By perpetuating this process you stand to do great harm to people worldwide as the United States lead will likely be followed. Putting research policy decisions in the hands of nonexperts in such a controversial and incredibly complex disease has no possible merit. Ignoring the 60 most experienced medical researchers is an utterly unacceptable plan for addressing a disease that robs people of their ability to live normal lives. Just because youre told and paid to do it doing your job doesnt excuse harming a million of your fellow citizens. Use scientific rigor to think about what youre doing. Stand up stop the P2P.</p>	<p>Thank you for sharing your story. The organization of the P2P workshop and process is beyond the scope of this report. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded this discussion. We erred on the side of being more inclusive with the case definitions as there is no agreed upon gold standard.</p>

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 27, 29 Patient's relative	General	I am writing to protest the entire P2P process including the production of this report. I have watched a loved one suffer with ME for over 7 years and am outraged at the US Department of Health Human Services HHS pretense that P2P is responsive to the Chronic Fatigue Syndrome Advisory Committee CFSAC October 2012 recommendation to convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition useful for research diagnosis and treatment. In no way is the P2P process responsive to this recommendation. NIH has not engaged or involved stakeholders in a substantive way. The Workshop panel consists of individuals with no expertise in ME or CFS. It ignores the subsequent letter to HHS by disease experts who have adopted the Canadian Case Definition for research to be updated as needed. Instead the focus of the draft report is medically unexplained fatigue. By using evidencebased practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possible worse than what has already been inflicted on people like my cousin. For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purposes.	Thank you for sharing your story. Please note that experts and patients were included as members of our technical expert panel in order to help guide the meaningfulness of the report. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded this discussion.
Public Reviewer # 48	General	I want to state in the strongest terms possible that I vehemently oppose and protest the acceptance of this Draft Report. This Draft Report is devastating to M.E. patients and effectively winds the clock backwards 30 years in terms of scientific advancement and understanding of the disease M.E. The entire premise of this review is deeply flawed and it can be summed up by quoting page ES30 as follows Given the breadth of symptoms in MECFS we a priori elected to not review symptom related outcomes except for fatigue. Some interventions may have revealed benefit for other characteristics of MECFS and this review would not have identified these outcomes. Are you serious Who gave you the authority to decide that you could focus solely on fatigue and ignore every other symptom related outcome Speaking with the authority of someone who has M.E. I can tell you that M.E. is not about fatigue You have been duped along with so many others by incorrectly paying attention to the name Chronic Fatigue Syndrome and letting it fool you into thinking that this illness revolves around fatigue. It does not People with M.E. experience much more than fatigue. Many of us suffer from terrible widespread musculoskeletal and/or Central Pain cognitive dysfunction profound weakness orthostatic intolerance and PEM postexertional malaise. Fatigue is the least of our problems By focusing solely on fatigue outcomes your conclusions are irreparably flawed. How could you summarily dismiss the crucial biomedical research pointing to defects in the immune system failed 2 day exercise tests autoimmune clues from the positive response to Rituximab in 60 of M.E. patients and so many other valuable findings that not only offer potential gold standard biomarkers but also prove that M.E. is an organic illness and not	Thank you for sharing your story and your comments. In consultation with the working group we elected to focus this review on the syndrome of ME/CFS which does not negate or under value the individual symptoms that patients experience. Fatigue was the one symptom that was universally identified in all of the case definitions which is why it was included along with other non-symptom based outcomes (function, employment, quality of life, etc.). Review of intermediate outcomes such as biomarker and cardiopulmonary testing was beyond the scope of this review. Additional invited guests and experts will be speaking at the P2P workshop to help inform the panel particularly on areas not addressed in this report.

Commentator & Affiliation	Section	Comment	Response
		<p>somatoform or some other psychosomatic disorder That you would arrive at the conclusion that Although CBT and GET have shown benefit in some measures of fatigue function and global improvement most other interventions have insufficient evidence to direct clinical practice page ES32 it reveals that you have a strong bias toward CBT and GET and gave no serious consideration to interventions that might successfully treat the underlying condition. I am not surprised that you arrived at this conclusion given that you only studied fatigue as an outcome. This however is a dangerous and damaging conclusion for people with M.E. to imply that clinicians continue to rely on CBT and GET. It returns us to the 20th century with regards to clinical treatment and it puts patients medical insurance and disability reimbursements in jeopardy. Do you deem this helpful to patients From my point of view you are only helping insurance companies and the government avoid immediate liability nevermind the fact that perpetuating these conditions by leaving them untreated and the spread unmitigated will only lead to astronomical increases in longterm expenses for these same 3rd party entities.In general I support the comments and conclusions of hundreds of other patient advocates as described by Mary Dimmock et al in a document entitled Comments on the AHRQ Evidence Review Diagnosis and Treatment of Myalgic Encephalomyelitis Chronic Fatigue Syndrome Dated October 18 2014In addition to the points made in that document I offer several points in my own words which are supported by my wife of 15 years and others involved in my daytoday care.I was appalled to see the list of studies that the 2 study investigators excluded for this Draft Review. At a minimum the investigators should have included rather than excluded the following studies Fluge O. 2011 Rituximab intervention Snell C. 2007 and additional work advocating the 2 day CPET testing protocol Fletcher MA. 2010 Plasma neuropeptide Y as a potential biomarker13 studies by Lenny Jason 4 papers by Tom Kindlon especially 2 in 2011 that challenged the use of GETCBTThese studies alone would and should have drastically altered the investigators conclusions. I will acknowledge and offer my appreciation that the 2 study investigators put a lot of time and effort into this Draft Review. But I want to remind you all that this Draft Review process is more than an academic exercise. It affects real people. People who are suffering every day from a terrible condition that will likely last a lifetime without pharmacological intervention and whose conditions will remain despite behavioral therapy. In my opinion the study investigators were overly rigid in their academic pursuit and seemed too eager to dismiss material that I would argue is extremely valuable for establishing diagnostic protocols and clarification of case definitions for M.E. For example on page ES25 the investigators state Much research in this field focuses on discovering etiologies rather than testing diagnostic strategies. Articles that attempted to define an etiology on the basis of a biochemical marker or a particular physiologic test were not included in this review because the intent of</p>	

Commentator & Affiliation	Section	Comment	Response
		<p>these was to identify an etiology rather than understand how the specific test could distinguish patients that would respond to treatment. So let me get this straight. Years and years of valuable research are just thrown out the window because of a technicality related to the investigators opinion about the researchers intent I argue that these excluded studies should be considered otherwise the conclusions are incomplete misleading and harmful to patients. Another example where the investigators were too nitpicky relates to their statement on page ES26 The MECFS literature is beginning to test diagnostic strategies but as yet has not presented data that would sufficiently differentiate the diagnosis of MECFS from other similar conditions in a population of patients with substantial diagnostic uncertainty. For example a proposed test might sufficiently distinguish a patient with CFS from one without but may not be able to distinguish between a patient with CFS and one with depression or rheumatoid arthritis conditions that a clinician might be considering simultaneously and attempting to rule out in a patient who presents with fatigue. This is a valid point but it is not a point that should disqualify these studies from consideration for this Draft Review rather it belongs on page ES31 under the section Future Research What are the future research needs for definition diagnosis and treatment of MECFS I would argue that these diagnostic clues are useful right now to both clinicians and researchers and these studies should have been included for purposes of this Review. In a realworld setting a clinician could use these diagnostic tests and clues to first establish that a patient indeed has abnormal labtest findings and that they meet certain diagnostic criteria for M.E. then the clinician could apply additional screening tools to differentiate between other conditions such as depression R.A. etc. before concluding that the patient indeed meets the case definition of M.E. and not some other condition. But according to this Draft Review the clinician should ignore these diagnostic tools because they arent specific enough to M.E. That is absurdI want to point out another flaw in the investigators application of the inclusionexclusion criteria. Specifically the 2011 study in Norway on Rituximab was excluded on the basis of failing to meet the 12 week duration criterion. It is obvious that for the purposes of this study the drug recipients would not be receiving more than 12 weeks worth of infusions however the study did follow the patient outcome for more than 12 weeks and therefore the results should have been considered and applied in the conclusions of this Review. Page ES30 states To evaluate the effectiveness and harms of interventions we elected to include studies of 12 weeks or longer duration due to the cyclical nature of the condition. Notably often antiviral or antibiotic medications</p>	

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #69	General	I am writing to protest the entire P2P process including the production of this report. Someone very dear to me has had ME for 7 years and I am outraged at the US Department of Health Human Services HHS pretense that P2P is responsive to the Chronic Fatigue Syndrome Advisory Committee CFSAC October 2012 recommendation to convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition useful for research diagnosis and treatment. In no way is the P2P process responsive to this recommendation. NIH has not engaged or involved stakeholders in a substantive way. The Workshop panel consists of individuals with no expertise in ME or CFS. It ignores the subsequent letter to HHS by disease experts who have adopted the Canadian Case Definition for research to be updated as needed. Instead the focus of the draft report is medically unexplained fatigue. By using evidence based practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possible worse than what has already been inflicted on people like me. For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purposes.	Thank you for sharing your story. The organization of the P2P workshop and process is beyond the scope of this report. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded this discussion.
Public Reviewer # 28	General	In October 2012 the Chronic Fatigue Syndrome Advisory Committee CFSAC made a unanimous recommendation to convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition useful for research diagnosis and treatment. But the US Department of Health Human Services HHS NIHs P2P process does not meet this recommendation because 1 it has not engaged or involved stakeholders experts patients and advocates in any substantive way and 2 it ignores the sixty most experienced medical researchers in this field relying instead on a panel with no expertise in either ME or CFS. The people with this disease I am one of them deserve better. Give us a voice in the process and include those doctors and scientists who have already immersed themselves in the research to help us find relief. Doing otherwise which is precisely what the P2P does is a gross failure of duty.	Thank you for sharing your story. The organization of the P2P workshop and process is beyond the scope of this report. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded this discussion.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 29	General	I am writing to protest the entire P2P process including the production of this report. My sisterinlaw has suffered with ME for more than 7 years and I am outraged at the US Department of Health Human Services HHS pretense that P2P is responsive to the Chronic Fatigue Syndrome Advisory Committee CFSAC October 2012 recommendation to convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition useful for research diagnosis and treatment. In no way is the P2P process responsive to this recommendation. NIH has not engaged or involved stakeholders in a substantive way. The Workshop panel consists of individuals with no expertise in ME or CFS. It ignores the subsequent letter to HHS by disease experts who have adopted the Canadian Case Definition for research to be updated as needed. Instead the focus of the draft report is medically unexplained fatigue. By using evidencebased practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possible worse than what has already been inflicted on people like me. For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purposes.	Thank you for sharing your story. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded this discussion. All of the case definitions were considered in order to provide a comprehensive summary of the current evidence and identify the limitations including those surrounding the case definitions.
Public Reviewer # 30	General	The P2P process is secretive befitting of a totalitarian society and nonscientific in its deliberate exclusion of experts. It in no way fulfills the recommendation of the October 2012 Chronic Fatigue Syndrome Advisory Committee CFSAC that HHS convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition to be used for research diagnosis and treatment. This uninformed workshop panel sits in defiance of ME experts who in their letter to HHS call for the immediate adoption of the Canadian Case Definition for research to be updated as needed. Instead the focus of the draft report is medically unexplained fatigue. By using evidencebased practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possibly worse than what ME patients have had to endure for decades. For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purposes. My thanks to Liz Willow and all those activists who have used their precious energy to elucidate and protest this travesty.	Thank you for sharing your story. The organization of the P2P workshop and process is beyond the scope of this report. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded this discussion.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 31	General	In the Draft AHRQ staff are correct that there is no gold standard test to assess any diagnostic test biomarker or case definition against. However this type of comparison is only one type of validity that is criterion validity. Other types of validity convergent divergent predictive content concurrent can still be used to assess diagnostic tests and criteria and should be encouraged explored in the absence of a gold standard. For example if researchers found a symptom group within MECFS that correlated consistently with specific testing cytokines neuroimaging exercise testing that test could help identify that group. Likewise if specific tests could predict outcome for a specific MECFS group it should also be considered.	Thank you for your comments. We included biomarker studies if they reported on diagnostic validity such as concordance, etc. We did not consider diagnosis of individual symptoms (such as PEM).
Public Reviewer #32	General	The P2P process is secretive befitting of a totalitarian society and nonscientific in its deliberate exclusion of experts. It in no way fulfills the recommendation of the October 2012 Chronic Fatigue Syndrome Advisory Committee CFSAC that HHS convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition to be used for research diagnosis and treatment. This uninformed workshop panel sits in defiance of ME experts who in their letter to HHS call for the immediate adoption of the Canadian Case Definition for research to be updated as needed. Instead the focus of the draft report is medically unexplained fatigue. By using evidencebased practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possibly worse than what ME patients have had to endure for decades. For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purposes. My thanks to patient [name redacted] and all those activists who have used their precious energy to elucidate and protest this travesty.	Thank you for sharing your story. The organization of the P2P workshop and process is beyond the scope of this report. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded this discussion.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 33	General	I am writing to protest the entire P2P process including the production of this report. I have had ME for 31 years and am outraged at the US Department of Health Human Services HHS pretense that P2P is responsive to the Chronic Fatigue Syndrome Advisory Committee CFSAC October 2012 recommendation to convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition useful for research diagnosis and treatment. In no way is the P2P process responsive to this recommendation. NIH has not engaged or involved stakeholders in a substantive way. The Workshop panel consists of individuals with no expertise in ME or CFS. It ignores the subsequent letter to HHS by disease experts who have adopted the Canadian Case Definition for research to be updated as needed. Instead the focus of the draft report is medically unexplained fatigue. By using evidencebased practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possible worse than what has already been inflicted on people like me. For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purposes.	Thank you for sharing your story. The organization of the P2P workshop and process is beyond the scope of this report. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded this discussion.
Public Reviewer # 34	General	I am glad AHRQ staff paid attention to the poor reporting of harms by the PACE and other GET CBT trials. Of note the bar for serious adverse events was unusually high for example subjects needed to have deteriorated for at least 4 weeks to be considered seriously affected so that if someone was bedridden for 2 weeks it would not qualify. Yet many clinicians not to mention patients and caregivers would consider that a serious adverse effect. White PD Goldsmith KA Johnson AL et al on behalf of the PACE trial management group. Appendix to Comparison of adaptive pacing therapy cognitive behaviour therapy graded exercise therapy and specialist medical care for chronic fatigue syndrome PACE a randomised trial. Lancet. 2011;377:2336. Whenever a treatment is reported in studies to be helpful but patients and clinicians report it doesn't work and may even cause harm everyone needs to be mindful of that. The clinic and not the research setting is where the rubber hits the road. There are several other factors AHRQ staff should consider in their assessment of the PACE trials a Posthoc analyses and reporting The PACE authors published their protocol years before the trial was started. Some outcomes they measured which were supposed to be reported like the self-paced step fitness test and Likert scale of Fukuda CFS symptoms were dropped without an explanation. They also lowered the threshold for deeming someone recovered and increased the threshold for SF36 score changes change from decrease over one assessment to over two to deem someone adversely affected. White PD Sharpe MC Chalder T DeCesare JC Walwyn R PACE trial group. Protocol for the PACE trial a randomised controlled trial of adaptive pacing cognitive behaviour therapy and graded exercise as	Thank you for your comments. We have also expanded our discussion of the limitations of this and other studies, particularly regarding harms reporting and the discussion of recovery as an outcome including the SF-36 threshold elected by the investigators.

Commentator & Affiliation	Section	Comment	Response
		<p>supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndromemyalgic encephalomyelitis or encephalopathy. BMC Neurol. 2007 Mar 876. b Wrong comparator group The original threshold for recovery was a SF36 physical function score of equal to or over 85. However by the time of publication the authors had changed the definition of recovery to mean a SF36 PF score of equal to or over 60. The PACE authors mentioned that they changed the score because half the workingage population would have SF36 scores below 85. However the PACE authors calculated their threshold by taking the mean scores from a large UK population assessed by Bowling et al. and subtracting off it by one standard deviation. The scores they used were based on a wide range of ages from 16 to over 85 including those who were working as well as the retired unemployed and unhealthy. The mean age of subjects in the PACE study were 3739 using the same SF36 guide Bowling 1999 and the same schema the threshold should have been 80 mean of 93.3 SD 13.3. Bowling A Bond M Jenkinson C Lamping DL. Short Form 36 SF36 Health Survey questionnaire which normative data should be used Comparisons between the norms provided by the Omnibus Survey in Britain the Health Survey for England and the Oxford Healthy Life Survey. J Public Health Med. 1999 Sep21325570.White PD Goldsmith K Johnson A L Chalder T Sharpe M. Recovery from chronic fatigue syndrome after treatments given in the PACE trial. Psychol Med. 2013 Oct 4310222735.c Priming of subjects On page ES28 AHRQ staff talk about expectation theory. This might also play a hand in why the PACE trial results are so different from what is reported outside of trials by patients and clinicians. The GET therapist manual instructs therapists that deconditioningp.23 is behind all the symptoms of MECFS while the CBT therapist manual attributes MECFS to interpretation.....and fear of symptoms p. 13 rather than any physiological issues. Consequently subjects are told that symptoms are a natural reaction to exercise and that in fact tiredness and some symptoms are needed to expect improvement. p. 53 GET participant manual. Subjects are also told that prior research shows most subjects get better or very much better with GET p. 28 GET participant manual. httpwww.pacetrials.orgtrialinfo Thus it is not entirely surprising that subjective outcomes would show improvement. However when objective outcomes are measured like the 6minute walk test 6MWT which was the only objective outcome examined in PACE the improvement seen leaves much to be desired. The highest absolute amount walked 379 meters by the GET group is still well below 500 630 meters measured in younger and elderly healthy adults. Furthermore the 6MWT was originally developed to assess exercise tolerance in chronic lung and heart disease. It has not been welltested for MECFS there are concerns within the rheumatologic community that the 6MWT might not be a good measure for monitoring systemic disease which MECFS is the minimal</p>	

Commentator & Affiliation	Section	Comment	Response
		clinically important difference is not known especially important for patientcentered outcomes and subjects who are motivated can push themselves to achieve better results on a onetime test that they might be able to sustain in regular daytoday life. https://www.rheumatology.org/Practice/Clinical/Clinician/researchers/Outcomes/Instrumentation/SixMinuteWalkTest/6MWT/mwt32 https://www.thoracic.org/statements/resources/pfetsixminute.pdf Thank you for considering my comments. I hope that they will be helpful in improving the final report.	
Public Reviewer # 35	General	It is shameful that the medical community does not do more about Myalgic Encephalomyelitis. It is debilitating and its affects are wider than just those who directly suffer. Its a real concern. Its not imaginary and its not in the heads of those who fight it. It is however apparent that because its not one of those diseases around which money machines have been created it is being ignored. Shame on the medical community.	Thank you for sharing your comment. The purpose of this report is to inform the P2P panel so that a research agenda might be set.
Public Reviewer #70	General	I am writing to protest the entire P2P process including the production of this report. I have had ME for 25 years and am outraged at the US Department of Health Human Services HHS pretense that P2P is responsive to the Chronic Fatigue Syndrome Advisory Committee CFSAC October 2012 recommendation to convene a stakeholder workshop including experts patients and advocates to reach a consensus for a case definition useful for research diagnosis and treatment.In no way is the P2P process responsive to this recommendation. NIH has not engaged or involved stakeholders in a substantive way. The Workshop panel consists of individuals with no expertise in ME or CFS. It ignores the subsequent letter to HHS by disease experts who have adopted the Canadian Case Definition for research to be updated as needed. Instead the focus of the draft report is medically unexplained fatigue. This is outrageous. By using evidencebased practice the very research studies that could move the field forward are ignored. The report itself will unequivocally set back research and treatment and lead to continued harm to patients quite possible worse than what has already been inflicted on people like me.For these reasons I object to the continuance of the P2P process including publication of this report its dissemination to the P2P panel and its use for any other purposes.	Thank you for sharing your comments. The organization of the P2P workshop and process is beyond the scope of this report. One of the goals of this review is to highlight the gaps in the current research and provide recommendations for future research. We have expanded this discussion.
Public Reviewer # 36	General	I urge AHRQ to correct the errors identified by Jennie Spotila et al. Tom Kindlon and Public Reviewer # 39 https://dl.dropboxusercontent.com/u/57025850/Comments20on20AHRQ20Evidence20Review20Part201of220Final.pdf https://dl.dropboxusercontent.com/u/57025850/Comments20on20AHRQ20evidence20review20Part202of220Final.pdf http://www.twitlonger.com/show/1sd5m0a https://drive.google.com/file/d/0B4uDVyWmlw2bUt0LWlnMz1Um8/viewpli1	Thank you - these comments have been addressed.
Public Reviewer # 37	General	Numerous researchers have documented the pattern by which individuals with severe forms of ME/CFS are excluded from research. Such individuals are also	Thank you for sharing your comments. We have followed sound methodology

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		<p>frequently excluded from stakeholder participation in the processes which determine their quality of life and life expectancy: AHRQ has ignored the disabilities/impairments (for example postexertional neuroimmune exhaustion and neurosensory disturbances, including sensory overload) experienced by individuals with ME/CFS; AHRQ has not provided all individuals with ME/CFS adequate time to read and/or listen to its ME/CFS draft and provide due commentary.</p> <p>By these actions, AHRQ has discriminated against individuals with ME/CFS; AHRQ has denied individuals with ME/CFS equality of opportunity; AHRQ has excluded individuals with ME/CFS from full and effective participation and inclusion in society; AHRQ has failed to respect the inherent dignity of individuals with ME/CFS, including their freedom to make their own choices and live independently of medical tyranny.</p> <p>AHRQ has failed individuals with ME/CFS. AHRQ has endorsed actions (CBT/GET), so called "therapies", which are known to be harmful. Due in part to such "therapies" and the attitudes of those who enforce them, internationally-honored Norwegian physician and medical ethicist Professor Ola Didrik Saugstad has said that individuals with ME/CFS are treated as horribly as individuals in the 1950's and '60s whom medical practitioners lobotomized (TV2.no, 2011). AHRQ has endorsed institutional abuse, and if not corrected, AHRQ's present draft will contribute even more heavily to the physical harm and prolonged psychological trauma of individuals with ME/CFS.</p> <p>At the 2014 IACFSME International Conference, researchers presented work on psychological trauma of individuals with ME/CFS, caused by widespread abuse across social institutions. Researchers defined social institutions as "the complex social forms that are found within governments, family, universities, hospitals, incorporated entities, legal systems and other social structures and organisations."</p> <p>Hallmann et al. state, "Relationships of power, politics, policies, practices and social relations were revealed to play an important role in the experience of ME/CFS. Trauma appeared to occur across every facet of the participant's lives, particularly in dealings with the medical profession, insurance companies, educators, employment, family, friends and the media."</p> <p>"Insurance companies were identified as particularly intrusive and onerous and often questioned or denied the validity of the diagnosis."</p> <p>"When interacting with social institutions, persons with ME/CFS are subject to attitudes, beliefs, policies and behaviours (including bullying)... These experiences have an adverse impact upon the person – both physically and emotionally."</p> <p>Dealings with social institutions "of this type and duration has been shown to impact individuals and cause long term trauma."</p>	<p>for conducting systematic reviews. Additionally, we included patients and experts on our Technical Expert Panel and throughout the review process had on our team a consultant who is an expert in ME/CFS.</p>

Source: <http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2004>
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		<p>In dealing with social institutions, individuals with ME/CFS commonly report “experiences of dishonesty, misstatement, threats, trauma, bullying and harassment... Such experiences were emotionally stressful and upsetting, whilst also causing exacerbation of the symptoms of the condition. The more stressful the event, the greater the potential severity of the symptom exacerbation.”</p> <p>Hallmann et al. identify further difficulties experienced by individuals with ME/CFS as: “assessments by persons with little knowledge of ME/CFS or preconceived and adverse beliefs about the condition, [and] inappropriate methods of assessing disability/impairment...”</p> <p>Hallmann et al. state as well that social institutions are ignorant of or ignore disabilities/impairments common to individuals with ME/CFS [postexertional neuroimmune exhaustion and neurosensory disturbances]; for example, a significantly lowered threshold to light and/or sound and a limited threshold to standing and/or sitting.</p> <p>Hallmann et al. further state that due to widespread ignorance and prejudice, individuals with ME/CFS generally don't have access to individuals to advocate for them and help them navigate social institutions. Further findings suggest parallels between individuals with ME/CFS and other disadvantaged/discredited social groups.</p> <p>G. Hallmann, R. Coutts, Y. Hartmann; “ME/CFS: Trauma in the Context of Social Institutions”, “ME/CFS: Social Security Accessibility and Experiences”, “ME/CFS: Institutional Dependence” (2014). http://www.iacfsme.org/DesktopModules/DigitalDownload/2014Syllabus25.pdf</p> <p>Research has shown elevated rates of PTSD among individuals with ME/CFS. Moreover, women in general, are at greater risk than men of developing PTSD. “ME/CFS affects women at six times the rate of men... [W]omen exhibit more severe fatigue, worse physical functioning, more bodily pain, poorer emotional functioning and significantly greater impairment of work activities...”</p> <p>The United Nations Convention on the Rights of Persons with Disabilities recognizes that “women and girls with disabilities are often at greater risk, both within and outside the home of violence, injury or abuse, neglect or negligent treatment, maltreatment or exploitation”.</p> <p>EJ Dansie, P Heppner, H Furberg, J Goldberg, D Buchwald, N Afari; “The Comorbidity of Self-Reported Chronic Fatigue Syndrome, Post-Traumatic Stress Disorder, and Traumatic Symptoms” (2012) http://www.nimh.nih.gov/health/topics/post-traumatic-stress-disorder-ptsd/index.shtml</p> <p>“Results from the Canadian Community Health Survey (CCHS) 2005, 2010 and 2012” http://www.meao.ca/files/Academic_Clinical_Perspectives.pdf http://www.un.org/disabilities/convention/conventionfull.shtml</p>	

Source: <http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2004>
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		<p>I urge AHRQ to address physical harms and psychological trauma experienced by individuals with ME/CFS, especially in regard to “therapy” protocols and false beliefs by medical personnel and insurers. I urge AHRQ to correct the errors identified by Jennie Spotila et al., Tom Kindlon, and Public Reviewer # 39: https://dl.dropboxusercontent.com/u/57025850/Comments%20on%20AHRQ%20Evidence%20Review%20Part%201of2%20Final.pdf https://dl.dropboxusercontent.com/u/57025850/Comments%20on%20AHRQ%20evidence%20review%20Part%202of2%20Final.pdf http://www.twitlonger.com/show/n_1sd5m0a https://drive.google.com/file/d/0B4uD-VyWmlw2bUt0LWInMzI1Um8/view?pli=1 And finally, I urge AHRQ to follow the advice of Thomas Sydenham. “In the seventeenth century Thomas Sydenham (1624-1689)... often referred to as the ‘English Hippocrates’, advocated classification of disease, not according to speculation or theory, but an accurate clinical description. Sydenham urged that the same attention to detail be taken in diagnosis of disease as botanists took in the classification of plants: ‘In the first place, it is necessary that all diseases be reduced to definite and certain species, and that with the same care which we see exhibited by botanists in their phytologies; since it happens, at present, that many diseases, although included in the same genus, mentioned with a common nomenclature, and resembling one another in several symptoms, are, notwithstanding, different in their natures, and require a different medical treatment’... [End Sydenham quote] [The word] Diagnosis...is derived from Greek meaning to distinguish or discern distinctive characteristics in precise terms... Progress in medicine results from increased discrimination... In general the more experienced the physician the less the observer error... It was Thomas Sydenham who first recommended ‘splitting’ rather than ‘lumping’: ‘We all know that the term thistle is applied to a variety of plants, nevertheless, he would be a careless botanist, indeed who contented himself with the general description of a thistle; who only exhibited the marks by which the class was identified; who neglected the proper and peculiar signs of the species, and who overlooked the characters by which they were distinguished from each other. On the same principle, it is not enough for a writer to merely note down the common phenomena of some multiform disease; for, although it may be true that all complaints are not liable to the same amount of variety, there are still many which authors treat alike, under the same heads, and without the shadows of a distinction, whilst they are in their nature as dissimilar as possible’.” [End Sydenham quote] Balint et al. 2006; Clin Rheumatol; “A brief history of medical taxonomy and diagnosis”</p>	

Factual and Conceptual Errors in the Executive Summary of the Draft Comparative Effectiveness Review "Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)" Raise Questions of the Review's Fitness for Purpose

October 3, 2014

A brief examination of the Executive Summary section of the Draft Comparative Effectiveness Review "Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)," prepared for the Agency for Healthcare Research and Quality (AHRQ) and published online September 22, 2014, reveals glaring factual and conceptual errors raising serious questions of the authors' qualifications and the fitness of their Review for its intended purpose. The Review is to be used as an allegedly objective knowledge base for the panel of non-experts at the upcoming Pathways to Prevention (P2P) Workshop on "ME/CFS."

The first paragraph of the Background section of the Executive Summary on page ES-1 states:

Myalgic encephalomyelitis (ME) and/or chronic fatigue syndrome (CFS) is a condition characterized by chronic and disabling fatigue as well as various additional manifestations including pain, sleep disturbance, neurological and cognitive changes, motor impairment, and altered immune and autonomic responses. [1-3] Experts consider post-exertional malaise (PEM) and memory or concentration problems critical components. [4] [Superscript reference numbers of the original are shown here in brackets.]

These are the references cited in the paragraph:

1. Carruthers BM, Jain AK, de Meirleir KL, et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. J Chronic Fatigue Syndr. 2003;11(1): 7-115.
2. Carruthers BM, van de Sande MI, De Meirleir KL, et al. Myalgic encephalomyelitis: International Consensus Criteria. J Intern Med. 2011;270(4): 327-38. PMID: 21777306.
3. Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med. 1994;121(12): 953-9. PMID: 7978722.7.

4. Jason LA, Brown A, Evans M, et al. Contrasting chronic fatigue syndrome versus myalgic encephalomyelitis/chronic fatigue syndrome. *Fatigue*. 2013;1(3)PMID: 23914329.

The use of the term "Myalgic encephalomyelitis (ME) and/or chronic fatigue syndrome (CFS)" raises some basic questions. The term presupposes an identity and common referent for the terms "ME" and "CFS" at the outset of the Review which is belied by one of the very references cited. Reference 2 is the 2011 Myalgic Encephalomyelitis: International Consensus Criteria (ME ICC) (Carruthers, 2011) developed by a highly qualified international panel of experienced doctors and biomedical researchers. The IC panel clearly states that ME and CFS should not be used to refer to the same condition, and further states that ME is not characterized by "chronic and disabling fatigue," as claimed by the Review authors. The ME ICC state:

Using 'fatigue' as a name of a disease gives it exclusive emphasis and has been the most confusing and misused criterion. No other fatiguing disease has 'chronic fatigue' attached to its name – e.g. cancer/chronic fatigue, multiple sclerosis/chronic fatigue – except ME/CFS. Fatigue in other conditions is usually proportional to effort or duration with a quick recovery and will recur to the same extent with the same effort or duration that same or next day. The pathological low threshold of fatigability of ME described in the following criteria often occurs with minimal physical or mental exertion and with reduced ability to undertake the same activity within the same or several days. (Carruthers, 2011, page 328)

The ME ICC characterize ME this way:

Myalgic encephalomyelitis is an acquired neurological disease with complex global dysfunctions. Pathological dysregulation of the nervous, immune and endocrine systems, with impaired cellular energy metabolism and ion transport are prominent features. Although signs and symptoms are dynamically interactive and causally connected, the criteria are grouped by regions of pathophysiology to provide general focus. (Carruthers, 2011, page 329)

In no legitimate way can this statement be construed to mean the subjective symptom of "fatigue." The ME ICC do not even list chronic fatigue as a necessary symptom for an ME diagnosis, let alone as a characterizing feature of the disease. It is a gross misrepresentation for the Review authors to cite the ME ICC as a reference for their misleading contention that ME and CFS refer to the same condition

"characterized by chronic and disabling fatigue." Using the ME ICC as a reference for this contention displays either an unfamiliarity with the cited reference or a deliberate attempt to mischaracterize the reference to support a contested statement when, in fact, the reference contradicts the statement. Such carelessness, at best, or intellectual dishonesty, at worst, should be sufficient disqualification for these authors as a source of accurate, reliable, and objective information.

Furthermore, the concluding sentence of the paragraph states, "Experts consider post-exertional malaise (PEM) and memory or concentration problems critical components. [4]" Reference 4 is a secondary, social science paper that again does not support the contention of the Review authors. Going to the primary definitional sources cited by the Review and used in Reference 4, Reference 1 is the 2003 Canadian Consensus Criteria for ME/CFS (CCC) (Carruthers, 2003). The CCC do not just consider PEM to be a "critical component," but more specifically an essential, necessary symptom for an ME/CFS, the term used by the CCC, diagnosis. Reference 3, the 1994 Fukuda case definition of CFS, lists PEM as one of eight optional symptoms for a CFS diagnosis – hardly a "critical component." Reference 2, the ME ICC, objects to the term "post-exertional malaise" (PEM) altogether:

'Malaise' – a vague feeling of discomfort or fatigue [41] – is an inaccurate and inadequate word for the pathological low-threshold fatigability and postexertional symptom flare. Pain and fatigue are crucial bioalarm signals that instruct patients to modify what they are doing in order to protect the body and prevent further damage. Postexertional neuroimmune exhaustion [PENE] is part of the body's global protection response and is associated with dysfunction in the regulatory balance within and between the nervous, immune and endocrine systems, and cellular metabolism and ion transport [42–46]. The normal activity/rest cycle, which involves performing an activity, becoming fatigued and taking a rest whereby energy is restored, becomes dysfunctional. [See the original paper for references cited.] (Carruthers, 2011, page 331)

Again, within a single paragraph, the Review authors have either carelessly or deliberately mischaracterized references to support questionable claims.

Still further, the following paragraph in the Executive Summary states:

The term ME was first used in the 1930s after an outbreak of neuromyesthesia [sic] and CFS was first coined in the 1980s. [5-7] Attempts to describe the condition based on possible underlying etiologies led to

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additional terms including post viral fatigue syndrome and chronic fatigue immune dysfunction syndrome. [1,3,5,6] The most recent international consensus report advocates moving away from the term CFS in favor of ME to better reflect an underlying pathophysiology involving widespread inflammation and neuropathology, and to embrace the two terms as synonymous. [2] However, others believe that ME is a subset of CFS and represents a more severe form of the same disease. [4] Some feel that the lack of specificity surrounding the name, CFS, may delegitimize and negatively characterize the condition, and stigmatize patients. [8] For this review, ME and CFS will be used synonymously (ME/CFS) and will include the populations(s) studied under either of these terms, recognizing that issues regarding terminology are currently unresolved.

The remaining references cited in this paragraph are:

5. Jason LA, Brown A, Clyne E, et al. Contrasting case definitions for chronic fatigue syndrome, myalgic encephalomyelitis/chronic fatigue syndrome and myalgic encephalomyelitis. *Eval Health Prof.* 2012;35(3): 280-304. PMID: 22158691.
6. Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: a working case definition. *Ann Intern Med.* 1988;108(3): 387-9. PMID: 2829679.
syndrome. *Metab Brain Dis.* 2013;28(4): 523-40. PMID: 22718491.
7. Ramsay M. *Myalgic Encephalomyelitis and Postviral Fatigue States: The saga of Royal Free disease.* 1st ed. London: Gower Medical Publishing; 1986.
8. Jason LA, Taylor RR, Plioplys S, et al. Evaluating attributions for an illness based upon the name: chronic fatigue syndrome, myalgic encephalopathy and Florence Nightingale disease. *Am J Community Psychol.* 2002;30(1): 133-48. PMID: 11928774.

The claim of the first sentence, "The term ME was first used in the 1930s after an outbreak of neuromyesthesia [sic] and CFS was first coined in the 1980s. [5-7]" is factually incorrect. The term ME was not used until the 1950s. The "outbreak of neuromyesthesia [sic]" in the 1930s presumably refers to an outbreak of polio-like illness, later considered to be ME, in Los Angeles in 1934 and well-documented by A. G. Gilliam in 1938 (Gilliam, 1938). Nowhere in the 1938 account is the term myalgic encephalomyelitis or ME used. To refer to the outbreak as "neuromyasthenia" is another anachronism, as the term was not used widely until the 1950s. Once again, if the Review authors had actually read the references they cite, it is unlikely they would make such obvious errors. Such academic sloppiness would not be acceptable in a PhD

dissertation, nor should it be acceptable in an important government report.

Nothing in Reference 4 justifies the statement in the Draft Review, "However, others believe that ME is a subset of CFS and represents a more severe form of the same disease. [4]" The statement in Reference 4, "Findings indicated that the ME-ICC identified a subset of patients with more functional impairments and physical, mental, and cognitive problems than the larger group of patients who met the Fukuda CFS criteria." (Jason, 2013) refers to patients meeting ME criteria as a subset of the specific group of patients, the set, recruited for the study meeting the broader 1994 case definition of CFS. Nowhere in Reference 4 do the authors speculate or state their belief that "ME is a subset of CFS and represents a more severe form of the same disease." Using Reference 4 to support the Review authors' contention that others believe ME to be a subset of the "same disease" CFS is unwarranted.

More troubling and further grounds to question the appropriateness of selecting the Review authors as a source of allegedly authoritative, objective knowledge for an even more unknowledgeable P2P panel is the following statement in the same paragraph:

The most recent international consensus report advocates moving away from the term CFS in favor of ME to better reflect an underlying pathophysiology involving widespread inflammation and neuropathology, and to embrace the two terms as synonymous. [2]

It is difficult to see this statement as other than a deliberate misrepresentation of the ME ICC designed to mislead the naive P2P panel. It is a shocking breach of intellectual integrity and surely grounds to disqualify the Review authors from completion of their contract. The ME ICC clearly recommend sole use of the term "myalgic encephalomyelitis" for patients meeting the ICC and removal of those patients from the broader, overly inclusive diagnostic category of CFS. Did the Review authors really expect no one would notice this egregious misrepresentation? What possible statement in the ICC would remotely suggest that the ICC authors would "embrace the two terms [ME and CFS] as synonymous"? The ICC authors do state that ME is "referred to in the literature as chronic fatigue syndrome (CFS)" however they clearly take exception to the confounding or combination of the two terms:

The label 'chronic fatigue syndrome' (CFS) has persisted for many years because of the lack of knowledge of the aetiological agents and the disease

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process. In view of more recent research and clinical experience that strongly point to widespread inflammation and multisystemic neuropathology, it is more appropriate and correct to use the term 'myalgic encephalomyelitis' (ME) because it indicates an underlying pathophysiology. It is also consistent with the neurological classification of ME in the World Health Organization's International Classification of Diseases (ICD G93.3). (Carruthers, 2011, page 327)

The ICC recommend that patients meeting the ICC be removed from the broader, overly inclusive CFS category in this statement: "Individuals meeting the International Consensus Criteria have myalgic encephalomyelitis and should be removed from the Reeves empirical criteria and the National Institute for Clinical Excellence (NICE) criteria for chronic fatigue syndrome." (Carruthers, 2011, page 334)

The authors of the ICC further elaborate this principle in the 2012 International Consensus Primer (ICP) (Carruthers, 2012):

Remove patients who satisfy the ICC from the broader category of CFS. The purpose of diagnosis is to provide clarity. The criterial symptoms, such as the distinctive abnormal responses to exertion can differentiate ME patients from those who are depressed or have other fatiguing conditions. Not only is it common sense to extricate ME patients from the assortment of conditions assembled under the CFS umbrella, it is compliant with the WHO classification rule that a disease cannot be classified under more than one rubric. (Carruthers, 2012, page ii)

The IC Primer also objects to labeling ME patients who meet the ICC with confusing hybrid terms containing the term CFS:

Misperceptions have arisen because the name 'CFS' and its hybrids ME/CFS, CFS/ME and CFS/CF have been used for widely diverse conditions. Patient sets can include those who are seriously ill with ME, many bedridden and unable to care for themselves, to those who have general fatigue or, under the Reeves criteria, patients are not required to have any physical symptoms. There is a poignant need to untangle the web of confusion caused by mixing diverse and often overly inclusive patient populations in one heterogeneous, multi-rubric pot called 'chronic fatigue syndrome'. We believe this is the foremost cause of diluted and inconsistent research findings, which hinders progress, fosters scepticism, and wastes limited research monies. (Carruthers, 2012, page ii)

The unsupported and unjustified claim that ME and CFS are synonymous terms opens the way for the authors of the Review to use

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unsound, invalid methodology for evaluating research studies and to use the obfuscating, ambiguous term "ME/CFS":

For this review, ME and CFS will be used synonymously (ME/CFS) and will include the populations(s) studied under either of these terms, recognizing that issues regarding terminology are currently unresolved.

This unsound methodology renders the entire Review valueless for comparing the merits of research studies done on disparate groups of subjects selected using various, widely differing case definitions. There is no rational way to determine the specific patient groups to which research results apply.

To claim the ICC authors "embrace" the two terms ME and CFS as "synonymous" is an outrageous breach of basic standards of professional writing by the Review authors. It is surely sufficient to indicate the remainder of the Draft Comparative Effectiveness Review is unreliable and untrustworthy. Just as a PhD candidate would be removed from a degree program for displaying such intellectual and ethical standards, the authors of this Draft Review have shown themselves to be unworthy of completing their work. The Agency for Healthcare Research and Quality should cancel their contract immediately to prevent the unreliable and ethically compromised work of these authors from being further legitimized by the US government.

References:

Carruthers BM, Jain AK et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. *J Chronic Fatigue Syndr.* 2003;11(1): 7-115.

Carruthers BM, van de Sande MI et al. Myalgic encephalomyelitis: International Consensus Criteria. *J Intern Med* 2011; 270:327–38. <http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02428.x/full>

Carruthers BM, van de Sande MI et al. Myalgic Encephalomyelitis – Adult & Paediatric: International Consensus Primer for Medical Practitioners. Published online October 2012. http://www.name-us.org/DefintionsPages/DefinitionsArticles/2012_ICC%20primer.pdf

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Gilliam, A. G. Epidemiological Study on an Epidemic, Diagnosed as Poliomyelitis, Occurring Among the Personnel of Los Angeles County General Hospital During the Summer of 1934. United States Treasury Department Public Health Service Public Health Bulletin, US Treasury Dept. No. 240. Washington, DC: United States Government Printing Office.1938.

Jason LA, Brown A, Evans M, et al. Contrasting chronic fatigue syndrome versus myalgic encephalomyelitis/chronic fatigue syndrome. *Fatigue*. 2013;1(3)PMID: 23914329.

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Comment on the Draft Report: Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

I wish to object most strongly to the AHRQ Evidence review 'Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)' which has been conducted in an extraordinarily unscientific manner. I have had about 40 years experience of close family members suffering from Myalgic Encephalomyelitis and so have experienced at first hand the damage and harm caused when different illnesses are confused. This type of confusion causes inconclusive research, misleading results and leads to patients being subjected to inappropriate management – causing irrevocable harm.

I object very strongly to the underlying assumption that patients included by the criteria of eight very different CFS and ME definitions have the same illness or subgroups of the same illness. They just do not. Research relating to a particular group of patients identified by the criteria of specific definition can not safely be applied to patients selected according to the criteria of a completely different definition. Some of these eight definitions actually exclude patients with other definitions included in this report! For example the Oxford CFS criteria excludes patients with signs of neurological illness – which are necessary for a Myalgic Encephalomyelitis diagnosis.

This absolutely basic flaw renders this review unscientific and utterly meaningless, by the most basic rules of logic and common sense. The deadly consequences of this type of confusion can be seen in the film 'Voices from the Shadows' <https://vimeo.com/ondemand/22513/108797012>
Patients with mild to moderate ME become patients with severe ME and may die when they are given behavioural/psychological based treatments appropriate for a different set of patients with chronic fatigue, because the underlying neuro-immune inflammatory pathology of the illness is ignored.

I wish to state my wholehearted agreement with the detailed 40 page submission by the parents, patients and advocates listed below –

Mary Dimmock
Claudia Goodell, M.S.
Denise Lopez-Majano, Speak Up About ME
Jennifer Spotila, J.D.
Lori Chapo Kroger, R.N., PANDORA Org CEO and President
Pat Fero, MEPD, President, Wisconsin ME & CFS Association, INC.
Darlene Fentner
Leonard Goodell, Jr.
Alan Gurwitt, M.D.
Wilhelmina D. Jenkins
Joseph Landson, M.S.
Margaret Lauritson-Lada
Jadwiga Lopez-Majano
Mike Munoz, PANDORA Org Board of Directors
Matina Nicholson
Charmian Proskauer
Mary M. Schweitzer, Ph.D.
Amy L. Squires, MPA
Susan Thomas
Erica Verrillo, Author

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20 October 2014 statement against AHRQ draft on ME/CFS:

Numerous researchers have documented the pattern by which individuals with severe forms of ME/CFS are excluded from research. Such individuals are also frequently excluded from stakeholder participation in the processes which determine their quality of life and life expectancy: AHRQ has ignored the disabilities/impairments (for example postexertional neuroimmune exhaustion and neurosensory disturbances, including sensory overload) experienced by individuals with ME/CFS; AHRQ has not provided all individuals with ME/CFS adequate time to read and/or listen to its ME/CFS draft and provide due commentary.

By these actions, AHRQ has discriminated against individuals with ME/CFS; AHRQ has denied individuals with ME/CFS equality of opportunity; AHRQ has excluded individuals with ME/CFS from full and effective participation and inclusion in society; AHRQ has failed to respect the inherent dignity of individuals with ME/CFS, including their freedom to make their own choices and live independently of medical tyranny.

AHRQ has failed individuals with ME/CFS. AHRQ has endorsed actions (CBT/GET), so called "therapies", which are known to be harmful. Due in part to such "therapies" and the attitudes of those who enforce them, internationally-honored Norwegian physician and medical ethicist Professor Ola Didrik Saugstad has said that individuals with ME/CFS are treated as horribly as individuals in the 1950's and '60s whom medical practitioners lobotomized (TV2.no, 2011).

AHRQ has endorsed institutional abuse, and if not corrected, AHRQ's present draft will contribute even more heavily to the physical harm and prolonged psychological trauma of individuals with ME/CFS.

At the 2014 IACFSME International Conference, researchers presented work on psychological trauma of individuals with ME/CFS, caused by widespread abuse across social institutions. Researchers defined social institutions as "the complex social forms that are found within governments, family, universities, hospitals, incorporated entities, legal systems and other social structures and organisations."

Hallmann et al. state, "Relationships of power, politics, policies, practices and social relations were revealed to play an important role in the experience of ME/CFS. Trauma appeared to occur across every facet of the participant's lives, particularly in dealings with the medical profession, insurance companies, educators, employment, family, friends and the media."

"Insurance companies were identified as particularly intrusive and onerous and often questioned or denied the validity of the diagnosis."

"When interacting with social institutions, persons with ME/CFS are subject to attitudes, beliefs, policies and behaviours (including bullying)... These experiences have an adverse impact upon the person – both physically and emotionally."

Dealings with social institutions "of this type and duration has been shown to impact individuals and cause long term trauma."

In dealing with social institutions, individuals with ME/CFS commonly report "experiences of dishonesty, misstatement, threats, trauma, bullying and harassment... Such experiences were emotionally stressful and upsetting, whilst also causing exacerbation of the symptoms of the condition. The more stressful the event, the greater the potential severity of the

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symptom exacerbation."

Hallmann et al. identify further difficulties experienced by individuals with ME/CFS as: "assessments by persons with little knowledge of ME/CFS or preconceived and adverse beliefs about the condition, [and] inappropriate methods of assessing disability/impairment..."

Hallmann et al. state as well that social institutions are ignorant of or ignore disabilities/impairments common to individuals with ME/CFS [postexertional neuroimmune exhaustion and neurosensory disturbances]; for example, a significantly lowered threshold to light and/or sound and a limited threshold to standing and/or sitting.

Hallmann et al. further state that due to widespread ignorance and prejudice, individuals with ME/CFS generally don't have access to individuals to advocate for them and help them navigate social institutions. Further findings suggest parallels between individuals with ME/CFS and other disadvantaged/discredited social groups.

G. Hallmann, R. Coutts, Y. Hartmann; "ME/CFS: Trauma in the Context of Social Institutions", "ME/CFS: Social Security Accessibility and Experiences", "ME/CFS: Institutional Dependence" (2014). <http://www.iacfsme.org/DesktopModules/DigitalDownload/2014Syllabus25.pdf>

Research has shown elevated rates of PTSD among individuals with ME/CFS. Moreover, women in general, are at greater risk than men of developing PTSD.

"ME/CFS affects women at six times the rate of men... [W]omen exhibit more severe fatigue, worse physical functioning, more bodily pain, poorer emotional functioning and significantly greater impairment of work activities..."

The United Nations Convention on the Rights of Persons with Disabilities recognizes that "women and girls with disabilities are often at greater risk, both within and outside the home of violence, injury or abuse, neglect or negligent treatment, maltreatment or exploitation".

EJ Dansie, P Heppner, H Furberg, J Goldberg, D Buchwald, N Afari; "The Comorbidity of Self-Reported Chronic Fatigue Syndrome, Post-Traumatic Stress Disorder, and Traumatic Symptoms" (2012)

<http://www.nimh.nih.gov/health/topics/post-traumatic-stress-disorder-ptsd/index.shtml>

"Results from the Canadian Community Health Survey (CCHS) 2005, 2010 and 2012"

http://www.meao.ca/files/Academic_Clinical_Perspectives.pdf

<http://www.un.org/disabilities/convention/conventionfull.shtml>

I urge AHRQ to address physical harms and psychological trauma experienced by individuals with ME/CFS, especially in regard to "therapy" protocols and false beliefs by medical personnel and insurers. I urge AHRQ to correct the errors identified by Jennie Spotila et al., Tom Kindlon, and [redacted for patient privacy]

<https://dl.dropboxusercontent.com/u/57025850/Comments%20on%20AHRQ%20Evidence%20Review%20Part%201of2%20Final.pdf>

<https://dl.dropboxusercontent.com/u/57025850/Comments%20on%20AHRQ%20evidence%20review%20Part%202of2%20Final.pdf>

http://www.twitlonger.com/show/n_1sd5m0a

<https://drive.google.com/file/d/0B4uD-VyWmlw2bUt0LWlnMzl1Um8/view?pli=1>

And finally, I urge AHRQ to follow the advice of Thomas Sydenham.

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“In the seventeenth century Thomas Sydenham (1624-1689)... often referred to as the ‘English Hippocrates’, advocated classification of disease, not according to speculation or theory, but an accurate clinical description. Sydenham urged that the same attention to detail be taken in diagnosis of disease as botanists took in the classification of plants: ‘In the first place, it is necessary that all diseases be reduced to definite and certain species, and that with the same care which we see exhibited by botanists in their phytologies; since it happens, at present, that many diseases, although included in the same genus, mentioned with a common nomenclature, and resembling one another in several symptoms, are, notwithstanding, different in their natures, and require a different medical treatment’ ...

[End Sydenham quote]

[The word] Diagnosis...is derived from Greek meaning to distinguish or discern distinctive characteristics in precise terms...

Progress in medicine results from increased discrimination...

In general the more experienced the physician the less the observer error...

It was Thomas Sydenham who first recommended ‘splitting’ rather than ‘lumping’:

‘We all know that the term thistle is applied to a variety of plants, nevertheless, he would be a careless botanist, indeed who contented himself with the general description of a thistle; who only exhibited the marks by which the class was identified; who neglected the proper and peculiar signs of the species, and who overlooked the characters by which they were distinguished from each other.

On the same principle, it is not enough for a writer to merely note down the common phenomena of some multiform disease; for, although it may be true that all complaints are not liable to the same amount of variety, there are still many which authors treat alike, under the same heads, and without the shadows of a distinction, whilst they are in their nature as dissimilar as possible.’ [End Sydenham quote]

Balint et al. 2006; Clin Rheumatol; “A brief history of medical taxonomy and diagnosis”

Sincerely,
Anonymous

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Comments on: Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Name: Tom Kindlon

Conflicts of Interest: I am Assistant Chairperson of the Irish ME/CFS Association. All my work for the Association is unpaid.

I agree that comments can be released, etc. – see disclosure statement below

My submission is a series of comments. Italics are used to represent quotes.

Comment #1: The Work and Social Adjustment Scale is not valid as an employment measure (or work impairment) and should not be used given actual employment data was reported for some studies.

Here are the questions that make up the Work and Social Adjustment Scale

Mundt JC1, Marks IM, Shear MK, Greist JH. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. Br J Psychiatry. 2002 May;180:461-4. <http://bjp.rcpsych.org/content/180/5/461.long>

Work and Social Adjustment Scale

Rate each of the following questions on a 0 to 8 scale: 0 indicates no impairment at all and 8 indicates very severe impairment.

- 1. Because of my [disorder], my ability to work is impaired. 0 means not at all impaired and 8 means very severely impaired to the point I can't work.*
- 2. Because of my [disorder], my home management (cleaning, tidying, shopping, cooking, looking after home or children, paying bills) is impaired. 0 means not at all impaired and 8 means very severely impaired.*
- 3. Because of my [disorder], my social leisure activities (with other people, such as parties, bars, clubs, outings, visits, dating, home entertainment) are impaired. 0 means not at all impaired and 8 means very severely impaired.*
- 4. Because of my [disorder], my private leisure activities (done alone, such as reading, gardening, collecting, sewing, walking alone) are impaired. 0 means not at all impaired and 8 means very severely impaired.*
- 5. Because of my [disorder], my ability to form and maintain close relationships with others, including those I live with, is impaired. 0 means not at all impaired and 8 means very severely impaired.*

Comment: Only one of these directly relates to work. This means that scores and in particular changes in scores during a trial (or between treatments) may have nothing to do with changes in employment.

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Comment #2:

The data from this paper, looking at employment outcome measures in the PACE Trial, were not used:

PLoS One. 2012;7(8):e40808. doi: 10.1371/journal.pone.0040808. Epub 2012 Aug 1. Adaptive pacing, cognitive behaviour therapy, graded exercise, and specialist medical care for chronic fatigue syndrome: a cost-effectiveness analysis. McCrone P1, Sharpe M, Chalder T, Knapp M, Johnson AL, Goldsmith KA, White PD. <http://www.plosone.org/article/info:doi/10.1371/journal.pone.0040808>

There are tables with various pieces of data. The authors summarise it as:
"There was no clear difference between treatments in terms of lost employment."

Comment #3:

Employment data were not reported in the draft ARHQ paper for the following study:

O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A. Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme. *Health Technol Assess.* 2006 Oct;10(37):iii-iv, ix-x, 1-121.
<http://www.journalslibrary.nihr.ac.uk/hta/volume-10/issue-37>

*"Group CBT did not significantly improve cognitive function, quality of life, *employment status* or healthcare utility measures"*

*"Group CBT did not significantly improve cognitive function, quality of life (as measured by the physical subscale of the SF-36), *employment status* or healthcare utility measures."*

Details:

Baseline pp87 (page 99 of pdf)

At 6 months: pp 99 (page 110 of pdf)

At 12 months: pp 106 (page 117 of pdf)

Comment #4:

Some other data from this study:

O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A. Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme. *Health Technol Assess.* 2006 Oct;10(37):iii-iv, ix-x, 1-121.
<http://www.journalslibrary.nihr.ac.uk/hta/volume-10/issue-37>

6 minute incremental shuttle walking test:

Physical performance – shuttles walked

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Similar trends were seen with the number of shuttles walked, as was seen for the GHQ scores, with more shuttles walked in the CBT treatment cohort and fewer in the SMC treatment cohort, with the EAS cohort showing results similar to the SMC group. Patients in the CBT cohort completed an average of 22 shuttles (200 m) compared with an average of 19 shuttles in the EAS treatment cohort and 18.3 in the SMC group (Table 7). Again, overall across the three groups the differences were not statistically significant ($p=0.16$), but the difference between CBT and SMC was nearing statistical significance ($p=0.060$). On average, patients in the CBT group completed 20% more shuttles than those randomised to SMC (odds ratio 1.20, 95% CI 0.99 to 1.45). As was seen for the other quality of life measures, the mean scores reported at 6 months were similar to those reported at 12 months ($p=0.80$) and the trend across the groups was unchanged between the 6- and 12-month assessments ($p=0.99$).

Five clear outlying observations were omitted from the analysis of shuttles walked. Three were very low values (0 or 2) and two were amongst the highest values (60 and 75), but were from a patient with a low baseline score (9). If these outliers were retained, the SEs increased and difference between CBT and SMC was no longer statistically significant ($p=0.17$).

The number of shuttles walked is illustrated in Figure 3. The distribution was positively skewed in each group, hence median scores are presented. The increase in the median number of shuttles walked in the CBT treatment condition from 20.5 (205 m) at baseline to 30 (300 m) at 12 months suggests an improvement, which did not reach statistical significance. The change from a median of 20.5 shuttles at baseline to 30 shuttles at 12 months in the CBT cohort represents an increase in walking speed at the end of the test from 2.64 to 3.02 miles per hour. The median increase is composed of an additional 4.5 shuttles at 2.64 miles per hour (level 5) and five shuttles at 3.02 miles per hour (level 6).

[My comment: I don't believe some or all of the outliers should be excluded. Scores of 60 and 75 are normal scores for healthy people - the paper says: "The ISWT, used as a physical performance measure, has normative reference data described by Taylor and colleagues. Their sample of 122 healthy subjects (mixed gender and age) walked a mean of 67 ×10-m shuttles" There is no reason that some people with CFS can't become healthy during a trial. Note that they appear not to have excluded other similar scores as they say "were among the highest" in "two were amongst the highest values (60 and 75)". These scores were only excluded because this person had a low score at baseline. But as I said, there is no reason why somebody couldn't improve during a trial.]

Comment #5:

The results of a walking test were mentioned for one study but not another:

Quote from draft:

*However, one trial also measured functioning using a walking speed test and found improved walking speed in the CBT group compared with controls (difference from baseline to 12 months for CBT vs. support: 1.77; 95% CI, 0.025 to 3.51; $p=0.0055$ and difference from baseline to 12 months for CBT vs. no intervention: 2.83; 95% CI, 1.12 to 5.53; $p=0.0055$).*⁸⁸

88=O'Dowd et al.

The following study had a 6-minute walking test and found no difference between CBT and the control group:

White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet*. 2011;377(9768): 823-36. PMID: 21334061.

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Comment #6:

Quote from draft:

79. Deale A, Husain K, Chalder T, et al. Long-term outcome of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. Am J Psychiatry. 2001;158(12): 2038-42. PMID: 11729022.

Draft has:

Three trials reported the number of hours, either per week or per 24-hours, individuals were working, with one trial reporting significantly more hours worked per week for the CBT group compared with relaxation (mean hours of 35.57 vs. 24.00 at 5 years; $p < 0.04$),⁷⁹

Hours worked per week at 5 years was higher in CBT group, mean (SD):35.57 (8.11) vs. 24.00 (4.97); $p < 0.04$ % With full-or part-time employment at 5 year followup: NS

Correction: the hours worked figure only apply to a sub-group. See Table 2 of Deale et al. (2001):

"Hours worked per week (employed patients only)"

Comment #7:

I'm dubious about the analysis regarding the harms of diagnosis. This [the harms of diagnosis] should really be compared to being in the same situation without any diagnosis. Instead, I think it combines/conflates two issues: the (i) harms of/problems caused by a diagnosis and (ii) the harms caused/problems caused from simply having the symptoms and impairments.

I believe without a diagnosis, it's harder to get support from family/friends/employers/education authorities/disability payers/etc., and it's more likely one will be incorrectly adjudged to be suffering from psychiatric problems. Also, somebody might be more likely to suffer from psychiatric problems (e.g. depression, anxiety, etc.) due to the lack of support of others than if somebody was diagnosed [with ME/CFS].

The CDC's 2003 population-based study

Reyes M, Nisenbaum R, Hoaglin DC, Unger ER, Emmons C, Randall B, Stewart G, Abbey S, Jones JF, Gantz N, Minden S, Reeves WC. Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas. Archives of Internal Medicine 2003;163:1530-1536
found that a delayed diagnosis was a risk factor for poor prognosis.

Woodward, Broom, and Legge found that obtaining a diagnosis was the single most helpful event in the search for social and medical legitimacy during the course of their illness.

Woodward RV, Broom DH, Legge DG. Diagnosis in chronic illness: disabling or enabling--the case of chronic fatigue syndrome. J R Soc Med. Jun 1995; 88(6): 325-329.

Comment #8:

There is a lot of talk of "functioning" (also "function"). I think the report needs to more clearly distinguish between self-reported functioning (which may be biased due to demand characteristics after undergoing therapy) and objective functioning. For example, in the

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PACE Trial, CBT reported higher physical functioning (as measured by the SF-36 physical function subscale) but no improvement on the 6-minute walking test over (i) APT and (ii) SMC alone.

Disclosure Policy for AHRQ Effective Health Care Program Public Review

Original Implementation Date: July 22, 2010; Most Recent Revision: July 29, 2014

The AHRQ Effective Health Care (EHC) Program supports and is committed to the transparency of its public review process. Reviewers are not required to provide their name or affiliation in order to submit comments.

For draft key questions, comments will be taken into consideration and may potentially result in modifications to the final key questions; however, individual comments will not be identified or posted, except in summary form.

For draft reports, comments will be publicly posted on the EHC Program Web site within 3 months after the associated final report is posted on this Web site. Each review comment on the draft report will be listed with the reviewer's name and affiliation, if such information is provided. Please note that if reviewers include identifiable personal health information, it will be redacted. The report authors' responses to the comments (the "disposition of comments") will be posted on the same Web page as the associated final report.

Acceptance of Disclosure Policy (Required for comment acceptance.)

I have read and understand the disclosure notice in the preceding paragraph and acknowledge that if I have made comments on a draft report, my comments will be posted on the EHC Program Web site with my name and affiliation, if submitted, within 3 months after this project's final report is posted on this Web site.

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Comments on “*Draft Comparative Effectiveness Review for Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)*”

By Charmian Proskauer, submitted 10/19/2014

I have three comments, two regarding the ratings given to evidence for the effectiveness of CBT and Graded Exercise Therapy in the draft report. **I feel strongly that these ratings should be re-evaluated, and downgraded in the final version of the report.** The other comment is about important work omitted in the reporting of harms.

Note: I suspect that the pre-established, pre-determined “objective criteria” used for these reports will preclude any corrections based on what is actually known about the condition of ME/CFS, but I hope that this is not true. If we present what little that has been scientifically studied as “what is known”, this will lead to a very skewed and misleading perception about this very serious illness.

FIRST COMMENT:

p. ES-12 “When combining all studies comparing any type of counseling to no treatment, support, relaxation, or adaptive pacing there is moderate strength of evidence that counseling improves fatigue (8/15 trials showed positive effect)”

My question is, if one takes at face value that 8 of 15 studies showed positive effect (and this could be argued in the case of the PACE trial), **how does 53% qualify as “moderate”?** That would seem to be “low” at best (since 47% of the trials showed no positive effect).

SECOND COMMENT:

p. 21-22 Harms were not well reported overall, and evidence is insufficient. Patients receiving GET reported more harms compared with cognitive behavioral therapy (CBT), adaptive pacing, or usual care in one good-quality trial and almost half of patients assigned to physiological exercise testing (10/25) refused to repeat testing at followup over concern for harm. Dropout rates were greater with exercise (25/68, 37%) than fluoxetine or placebo (15/69, 22%).

As the report itself notes, harms from GET, as implied from patient behavior in studies, are significant. I do not know of any scientific study which has measured this in a controlled way, nor do I believe such a study would be ethical. For further reports on harms from GET, please see [Reporting of Harms Associated with Graded Exercise Therapy and Cognitive Behavioural Therapy in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome](#), T. Kindlon, Bull. IACFS/ME: 19 (2), Fall 2011. This important paper was omitted from your review because it appeared in a non-indexed journal (“gray literature”). **The paper should be evaluated on its merits and its evidence for harms cited in the report.** This paper also documents several serious concerns with the methodology used in the PACE trial (see next). Furthermore, it would have been interesting to learn what would have happened if the PACE trial had required participants to repeat the final six-minute walk test one day later – given what we now know about “post-exertional malaise” in patients who have ME, how many would have refused to walk the second day, and what would have been the distances reached for those who did?

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THIRD COMMENT:

Table 3, p. 41.

"White, et al., 2011"⁹⁸

PACE Trial

N=480

Good"

Given the well-documented deficiencies of the PACE trial (granted, the studies documenting the deficiencies were not reviewed in this report), how can the PACE trial be rated as "Good"?

In addition to our previous comments/references supporting comments on the deficiencies of the PACE trial (quoted below for convenience) I would draw your attention to the following by Fred Friedberg, PhD, President, International Association for CFS/ME:

<http://iacfsme.org/PACETrial/tabid/450/Default.aspx>

IACFS/ME Statement on the PACE Trial: The Issue of Illness "Reversal" February 24, 2011

The much publicized UK-based PACE trial (*Lancet*, Feb. 18th; [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(11\)60096-2/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext)) reported positive outcomes for patients with CFS/ME who were treated with cognitive-behavior therapy (CBT) or graded exercise therapy (GET) in comparison to a standard medical care condition or an adaptive pacing condition. The adaptive pacing condition was intended to help patients adjust their activity levels according to their available energy (based on envelope theory). The findings were similar to previous CBT and GET studies in CFS. This trial was unique in incorporating a pacing condition and recruiting a very large sample. That said, we have concerns about how the trial was reported.

We certainly support any effective treatment for CFS/ME, medical or behavioral. Behavioral interventions are helpful for a number of major medical conditions (cardiovascular disease, diabetes).

Illness "Reversal" and Behavioral Intervention

The most fundamental concern we have is focused on the type of causal model that was linked to the CBT and GET conditions in this study. The model, based on the application of cognitive-behavioral and physical conditioning principles, predicts that properly designed behavioral or exercise interventions will "reverse" the CFS illness. Not improve symptoms/functioning or provide better management, but "reverse" the illness. This term implies that the illness can be cured (or something close to it) with behavioral techniques.

If one assumes such a direct correspondence between behavioral treatment and curative outcomes, then the illness is by implication a psychiatric condition. Once this assumption is made, then research efforts to assemble a biomedical model of CFS are more likely to be delegitimized. And the public's perception of the illness as simply being tired is again reinforced. Perhaps this is the most unfortunate aspect of the PACE trial: The omission of any reference to the medical complexity of this illness.

Furthermore, when one compares the study goal of illness "reversal" to the reported outcomes, the support for such reversal is modest at best: 30% of GET and CBT patients achieved normative physical functioning-- but the 30% figure was *in comparison to* 15% who achieved such normative function in the standard medical care control condition.

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Thus a more accurate statement of this finding would be: An additional 15% of patients in the CBT and GET conditions achieved normal functioning in comparison to standard medical care. The critical standard of clinical significance is that a therapy results in restoration of normal function. But their own data do not support reversal outcomes above and beyond standard medical care for the vast majority of their subjects in the CBT and GET conditions.

Question of CFS/ME Diagnosis

In addition, the 15% advantage over standard care for patients in CBT and GET can be further questioned given that at least 1/3 of all patients did not meet the strict international criteria for CFS (Table 1 in study)—the diagnostic protocol most often used in published studies. Strict criteria for CFS are linked to poor prognosis and conversely, subjects who don't meet strict criteria for CFS have better outcomes. So the PACE trial folded in a significant number of subjects who do not have CFS according to standard criteria. Again this dilutes the significance of their findings as it makes it more difficult to generalize to the population of people who do have CFS.

To put behavioral approaches in context—they can be quite helpful, but they hardly meet the standard of clinical significance that would elevate them to curative interventions. If this had been made clear in the study, it would have provoked far less controversy and debate.

Media Mis-reports

Finally, the media message from this study has often been: “Exercise is good; Rest is bad.” Although the PACE trial authors did not issue such a statement, I think there is some responsibility to explain to the media that this type of recommendation is simplistic and potentially harmful for patients with CFS/ME. Activity and exercise recommendations must be based on a thorough evaluation and a sensitive individualized approach, not the broad brush that has become the take home message of this study.

Fred Friedberg, PhD
President
IACFS/ME

Extract from our previous comments on the PACE trial

2(d). The Evidence Review failed to examine and report the deficiencies in the PACE trial. The PACE trial featured prominently in this Evidence Review.⁴ It is the largest of all the intervention trials examined, and it reported significant improvement on several outcome measures. However, the Evidence Review failed to examine any of the well-documented deficiencies in this study, which if considered would likely downgrade the Review's assessment of the trial.

First, the Evidence Review failed to connect its concerns about the Oxford definition (p. 77) with the subject selection criteria for PACE. The PACE authors used the Oxford definition, and excluded patients “at significant risk of self-harm.”⁴

While Oxford requires the exclusion of patients with psychosis, bipolar disorder, substance abuse, and organic brain disorder, it does not require the exclusion of patients with depressive or anxiety disorders. Indeed, a subsequent paper reported that 46% of the PACE subjects had anxiety, depression or both.³²

Another paper examined the patients enrolled from one PACE center and found that 56% of subjects had a co-morbid psychiatric disorder, including depression, anxiety, obsessive compulsive disorder, post-traumatic stress disorder, and phobias.³³

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The CBT and GET programs tested in the PACE trial would be predicted to benefit patients with primary psychiatric disorders. Whether the PACE treatments would benefit an ME cohort without co-morbid psychiatric disorders is an important and unresolved question.

In addition, the inclusion of patients without ME through the use of the Oxford definition calls into question whether the PACE results can be generalized to ME patients even if they have secondary depression or anxiety. Therefore, the applicability of the PACE results to patients with ME cannot be assumed.

Second, PACE relied heavily on self-report outcomes measures, and even discarded the original plan to measure subject activity through actigraphy.³⁴ In a follow-paper, inexplicably excluded from the Evidence Review, the PACE authors acknowledge that objective measures do not correlate well with self-report measures.³⁵

The objective measure reported in the PACE trial is the six minute walking test, with the biggest improvement reported in the GET arm of the trial (an increase of 67 meters over baseline 11 to 379 meters).⁴ However, the PACE authors fail to note that this improvement still left the subjects below the 400 meter threshold qualifying for lung transplantation.³⁶

The PACE authors have defended the poor results, pointing to variations from how the test is usually performed.³⁷ However, the fact remains that the improvements, even in the GET arm, were not remarkable and not indicative of gain of function.

Third, the follow-up paper on recovery in the PACE trial revealed several post hoc changes to data analysis.³⁵ The most startling is the definition of recovery with an SF-36 physical function score of 60 or less (reduced from the original threshold of 85 or less).³⁴ Given that the entry criteria for PACE included an SF-36 score of 65 or less, this change permits the outcome of patients being classified as “recovered” when in fact their physical function decreased from baseline. This threshold is also notable because the 2005 Reeves Empirical definition uses a diagnostic threshold of 70 or less on the same scale.³⁸

Finally, PACE data show that there was a slight increase in the number of participants receiving illness and disability benefits by the end of the trial.³⁹

Fourth, the PACE subjects were enrolled based on meeting the Oxford criteria, but were also assessed with the “international criteria” for CFS and the London criteria.⁴ It must be pointed out that the international criteria referenced by the authors was Reeves 2003,⁴⁰ and that the four symptoms required to accompany fatigue were only required to be present for one week.³⁵

There is also some controversy over whether the proper London criteria was used.⁴¹ The authors report that 67% of PACE participants met the modified CDC definition, and 51% met the London criteria.³⁵ However, these assessments were made on the Oxford cohort, not independent cohorts, and therefore it is difficult to draw conclusions about patients meeting other case definitions (including correctly applied Fukuda and London).

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The PACE trial results and subsequent publications have been very controversial. The Evidence Review did not include several of the follow-up papers, and assigned a “Good” quality rating without acknowledging or addressing the many flaws of the PACE trial:

- PACE used an overly broad definition that could include people with other causes of fatigue;
- almost 50% of PACE subjects had psychiatric disorders;
- objective measures of physical function showed minor or no improvement;
- recovery was redefined in such a way that patients who worsened from baseline could be counted as recovered; and
- application of additional diagnostic criteria was flawed.

Given these significant flaws, there is a danger of overstating the results of PACE, and certainly a high risk in drawing conclusions about whether PACE is applicable to ME patients. The Evidence Review should reexamine the PACE data, and reconsider its quality assessment.

Furthermore, the Evidence Review should interpret the PACE results with caution, particularly the strength of evidence assessments that include PACE.

⁴White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behavior therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomized trial. *Lancet*. 2011;377(9768): 823-36. PMID: 21334061.

³²Cella M, White PD, Sharpe M, et al. Cognitions, behaviours and co-morbid psychiatric diagnoses in patients with chronic fatigue syndrome. *Psychol Med*. 2013 Feb;43(2): 375-80. PMID: 22571806.

³³Lawn T, Kumar P, Knight B, et al. Psychiatric misdiagnoses in patients with chronic fatigue syndrome. *JRSM Short Rep*. 2010;1(4): 28. PMID: 21103120.

³⁴White PD, Sharpe MC, Chalder t, et al. Protocol for the PACE trial: a randomized controlled trial of adaptive pacing, cognitive behavior therapy, and graded exercise, as supplements to standardized specialist medical care versus standardized specialist medical care alone for patients with the chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy. *BMC Neurol*. 2007;7:6. PMID: 17397525.

³⁵White PD, Goldsmith K, Johnson AL, et al. Recovery from chronic fatigue syndrome after treatments given in the PACE trial. *Psychol Med*. 2013;43(10): 2227-35. PMID: 23363640.

³⁶Kadikar A, Maurer J, Kesten S. The six-minute walk test: a guide to assessment for lung transplantation. *J Heart Lung Transplant*. 1997;16(3): 313-9. PMID: 9087875.

³⁷White PD, Goldsmith K, Johnson AL, et al. Letter to the Editor: Response to correspondence concerning ‘Recovery from chronic fatigue syndrome after treatments in the PACE trial’. *Psychological Medicine*. 2013;43: 1791-1792. PMID: 23866117.

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³⁸Reeves WC, Wagner D, Nisenbaum R, et al. Chronic fatigue syndrome –a clinically empirical approach to its definition and study. BMC Med. 2005;3: 19. PMID: 16356178.

³⁹McCrone P, Sharpe M, Chalder T, et al. Adaptive pacing, cognitive behavior therapy, graded exercise, and specialist medical care for chronic fatigue syndrome: a cost-effectiveness analysis. PLoS One. 2012;7(8): e40808. PMID: 22870204.

⁴⁰Reeves WC, Lloyd A, Vernon SD, et al. Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. BMC Health Serv Res.2003;3(1): 25. PMID: 14702202.

⁴¹Goudsmit, EM. Rectification to ensure balance.
http://pb.rcpsych.org/content/early/2014/07/14/pb.bp.113.045005/reply#pbrcpsych_el_21243 (retrieved October 9, 2014).

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Clarification: AHRQ Draft Comparative Effectiveness Review #XX Sept.22, 2014 – Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Re Executive Summary, Background, page ES1, paragraph 2: This report states that the International Consensus Criteria advocate moving away from the term CFS in favor of ME ... and to embrace the two terms as synonymous.

Clarification: The International Consensus Criteria (ICC) advocate moving away from the term CFS in favor of ME for those patients meeting the widespread inflammation and multisystemic neuropathy that are characteristic of the underlying pathophysiology of myalgic encephalomyelitis.

However, **the International Consensus Criteria do NOT advocate embracing the two terms as synonymous.** The ICC point out the confusion and problems that have arisen from using broadly inclusive criteria that do not discriminate ME patients from those with other fatiguing conditions. The ICC advocate, **“Individuals meeting the International Consensus Criteria should be removed from the Reeves empirical criteria and National Institute for Clinical Excellence (NICE) criteria for chronic fatigue syndrome”.** (1, page 334)

The International Consensus Panel provides further clarification for the need to remove ME patients from the CFS umbrella in **MYALGIC ENCEPHALOMYELITIS – Adult & Paediatric: International Consensus Primer for Medical Practitioners. (2)**

“Misperceptions have arisen because the name ‘CFS’ and its hybrids ME/CFS, CFS/ME and CFS/CF have been used for widely diverse conditions... There is a poignant need to untangle the web of confusion caused by mixing diverse and often overly inclusive patient populations in one heterogeneous, multi-rubric pot called ‘chronic fatigue syndrome’.... Our panel strongly recommends that **only the name ‘myalgic encephalomyelitis’ be used to identify patients meeting the [International Consensus Criteria] ICC** because a distinctive disease entity should have one name. Patients diagnosed using broader or other criteria for CFS or its hybrids (Oxford, Reeves, London, Fukuda, CCC, etc.) should be reassessed with the ICC. Those who fulfill the criteria have ME; those who do not would remain in the more encompassing CFS classification.... Not only does it make sense to extricate ME patients from the assortment of conditions assembled under the CFS umbrella, it is compliant with the WHO classification rule that a disease cannot be classified under more than one rubric. The panel is not dismissing the broad components of fatiguing illnesses, but rather the ICC are a refinement of patient stratification. As other identifiable patient sets are identified and supported by research, they would then be removed from the broad CFS/CF category.” (emphasis added) (2, page ii)

1. Carruthers BM, van de Sande MI, De Meirleir KL, Klimas DG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Baumbarten-Austrheim B, Bell DS, Carlo-Stella N, Chia J, Darragh A, Jo D, Lewis D, Light AR, Marshall-Gradisnik S, Mena I, et al. **Myalgic encephalomyelitis: International Consensus Criteria.** *J Intern Med* 2011; 270: 327-338. [PMID: 21777306]
<http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02428.x/pdf>
2. Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Bell DS, Carlo-Stella N, Chia J, Darragh A, Gerken A, Jo D, Lewis D, Light AR, Light K, Marshall-Gradisnik S, McLaren-Howard J, Mena I, Miwa K, Murovska M, Steven S. Editors: Carruthers BM, van de Sande MI. **MYALGIC ENCEPHALOMYELITIS – Adult & Paediatric: International Consensus Primer for Medical Practitioners. 2012. ISBN 978-0-9739335-3-6**
http://www.name-us.org/DefintionsPages/DefinitionsArticles/2012_ICC%20primer.pdf

Sincerely,
Marj van de Sande,
Co-author/co-editor, ICC and ICP
October 14, 2014

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Comments on the AHRQ ME/CFS Diagnosis and Treatment Evidence Report

It is evident that the authors have devoted considerable time and attention to what is a very complicated area. Many of the suggestions that have been made in the report for ways of improving the data and studies for future evidence reviews will be helpful.

Nevertheless, there are a number of areas in the report that require further analysis, additional data and in some cases complete rethinking.

The comments that follow are not comprehensive.

In preparing these comments reference has been made to the *AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (CER's)* including chapter 5 (Finding evidence for comparing medical interventions), chapter 7 (Avoiding Bias in the Selection of Studies), and chapter 8 (Selecting Observational Studies for Comparing Medical interventions). These chapters clearly demonstrate that, even when great care is taken in preparing these CERs, there are always areas where questions will arise (including the search strategies employed, the studies which are selected and the inclusion and exclusion criteria) – and indeed, these are some of the areas where concerns have arisen.

Comments are bolded and in general precede the discussion. Quotes from the evidence report are in italics.

Comment One– Case definitions -- **The case definitions are not interchangeable. Treating them as such in the review ignores the evidence about differences in patient populations.**

Selected references from Evidence Review (in italics)

p. 1 *“Currently diagnosing a patient with ME/CFS relies on the use of a set of clinical criteria (case definitions) to distinguish ME/CFS from other conditions that may also present with fatigue.”*

Results (Structured Abstract) V -- *“Multiple case definitions have been used to define ME/CFS and those that require the symptoms of post-exertional malaise and neurological and autonomic manifestations appear to represent a more severe subset of the broader ME/CFS population”* (repeated in similar format in the Executive Summary ES-25 (... appear to represent ‘more involved’) and main report p. 60 (appear to represent ‘more impaired’)

ES- 1 and p.1 *“For this review, ME and CFS will be used synonymously (ME/CFS) and will include the population(s) studied under either of these terms, recognizing that issues regarding terminology are currently unresolved.”* [Underlining added.]

ES- 26 *Several studies attempted to demonstrate that ME, ME/CFS, and CFS case definitions identify different groups of people. Studies did this by identifying people who met one criteria but not the other. Using this approach, it appears that the case definitions labeled as ME and ME/CFS select a population with more impairment, lower functioning, and higher symptom reporting compared with the case definitions labeled as CFS alone.”*

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Conclusions ES-32: *“Multiple case definitions for ME/CFS exist with those that require symptoms of PEM, neurological impairment, and autonomic dysfunction representing a more severe form of the condition.”*

Discussion: The whole evidence review mixes and matches the definitions of ME and CFS. It identifies eight case definitions, notes that those with the labels ME and ME/CFS define a population that is more severely impaired and then treats them as essentially equivalent, which they are not. This approach was continued in the treatment sections, where treatments used for any of the case definitions were analyzed and results reported. One reason given in the review is to allow a “broad representation of patients.” This is not helpful when we are trying to properly diagnose and treat people with ME. They may need and respond to entirely different treatments.

The issues are not just of “terminology” they are at the basis of much of the existing confusion, underlie much of the current discussion and fuel current research.

In the Future Research section, the report suggests that “it would be ideal if future intervention studies consistently used an agreed upon single case definition.” Such an agreed upon definition has been put forward. **Approximately 50 researchers and clinicians signed an open letter to then US Secretary of Health and Human Services, the Honorable Kathleen Sebelius.** The original letter was dated September 23, 2013 and updated with additional signatures on October 25, 2013.

“We are writing as biomedical researchers and clinicians with expertise in the disease of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) to inform you that we have reached a consensus on adopting the 2003 Canadian Consensus Criteria (CCC) as the case definition for this disease”. [Underlining added.]

<https://dl.dropboxusercontent.com/u/89158245/Case%20Definition%20Letter%20final%2010-25-13.pdf>

The IACFS/ME has produced a Primer for physicians which is posted on the National Guidelines Clearinghouse website. It is based on the CCC [Canadian, Carruthers et al, 2003] definition.

International Association for Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis (IACFS/ME). Chronic fatigue syndrome/ myalgic encephalomyelitis. A primer for clinical practitioners. Chicago (IL): International Association for Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis (IACFS/ME); 2012. 41 p. [121 references]

National Guidelines Clearinghouse

<http://www.guideline.gov/content.aspx?id=38316#Section424>

Comment Two – Case definitions (continued) – Oxford, in particular

The review treats all definitions as if they are describing the same disease. The conclusions ignore the very shortcoming it highlights elsewhere – that is, that some definitions (Oxford in particular)

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may inappropriately include patients that would not otherwise be diagnosed with ME/CFS and may provide misleading results.

Reference in Review -- ES-29 Applicability *"We elected to include trials using any predefined case definition but recognize that some of the earlier criteria, in particular the Oxford (Sharpe, 1991) criteria, could include patients with 6 months of unexplained fatigue and no other features of ME/CFS. **This has the potential of inappropriately including patients that would not otherwise be diagnosed with ME/CFS and may provide misleading results.**" (emphasis added)*

Comment Three – Case definitions (continued) ME 1988 definition not included

Although Dr. Melvin Ramsay described ME in 1986 his definition was updated in 1988 – the cutoff year used for this review.

The ME case definition as described by Dr. Melvin Ramsay has not been included as one of the case definitions. The earlier version in 1986 is a general reference. On page 17 (3rd paragraph) Ramsay's name is misspelled as "Ramsey" in the description of one of the studies (Jason et al 2012)

Ramsay M: Myalgic Encephalomyelitis and Postviral Fatigue States. 2nd edition. London: Gower Medical Publishing; 1988.

Comment Four – Case definitions (continued) ME – ICC definition

The ICC definition is for Myalgic Encephalomyelitis (ME). It is for ME for a reason; because of what is known about ME and its underlying pathophysiological dysfunction.

Reference in Review p. 1 *"The most recent international consensus report advocates moving away from the term CFS in favor of ME ... and to embrace the two terms as synonymous."*

The ICC specifically seeks to distinguish ME from CFS as follows: "Individuals meeting the ICC have myalgic encephalomyelitis and should be removed from the Reeves empirical criteria and the National (NICE) criteria for chronic fatigue syndrome."

The publication of the ICC resulted in comment to the article (van der Meer and Lloyd) which resulted in a follow-up response (Broderick) which included the following statements providing more information about the importance of distinguishing the case definition.

"Whether patients with less severe conditions represent a continuum, faulty diagnosis or different disease entities can only be determined by future studies"

"When advances in scientific technology are applied to patients who meet the more specific case definition of the ICC for ME, the current urgent need for identifying and confirming

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specific biopathological mechanisms and biomarkers will be facilitated, and our improved understanding of the pathophysiology can then be directed towards enhancing treatment efficacy. “

van der Meer, J. W. M. and Lloyd, A. R. (2012), A controversial consensus – comment on article by Broderick *et al.* Journal of Internal Medicine, 271: 29–31. doi: 10.1111/j.1365-2796.2011.02468.x

Broderick, G. (2012), Response to ‘A controversial consensus’; By the International Consensus Panel. Journal of Internal Medicine, 271: 213–217. doi: 10.1111/j.1365-2796.2011.02499.x

Comment Five – Reconsider the exclusion of the studies looking at biomarkers, cell function, immunologic, virologic/bacterial hormonal etc. (See also comment eight, which deals with related issue)

Reference in Review -- ES -1 *“This review is not intended to address the question of etiology nor underlying factors that lead to the onset or perpetuation of ME/CFS but rather to focus on the diagnosis and treatment of this syndrome.”*

ES-25 *“Articles that attempted to define an etiology on the basis of a biochemical marker or a particular physiologic test were not included in this review because the intent of these was to identify an etiology rather than understand how the specific test could distinguish patients that would respond to treatment.”* As well, subgroups were not studied as they did not report diagnostic testing outcomes.

Discussion -- This is a chicken and egg proposition. Accurate diagnosis and treatment will rely on knowing more about the body’s response to ME/CFS. The review paper outright excludes some very important studies that are pointing to biomarkers as well as to other ways of distinguishing ME/CFS patients by subgroups. These papers are important stepping stones; not only to more precise diagnosis of ME/CFS patients but to appropriate treatment for the subgroups the research has begun to demonstrate.

Studies excluded include a large literature showing biologic abnormalities in persons with ME/CFS; a literature that directly links to the case definitions. Studies were excluded if they looked at any outcome other than fatigue i.e. pain, antidepressants, sleep treatment (see also comment eight).

One of the very interesting sections of the report starts on p. 74 **“Findings in Relationship to What is Already Known.”** Much of this section is also found in Key Findings and Strength of Evidence p. ES- 25 and on. This material is of considerable importance in providing a context for the larger picture as well as for future research. The [**Findings in Relationship to What is Already known**] section explains why the review does not look at the research which the study has determined is “focused at discovering etiologies rather than testing diagnostic strategies in patients.” This includes studies on biomarkers and studies on “cell function,

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immunologic, virologic/bacterial, hormonal etc” which identified subgroups on the basis of exercise testing, cerebral blood flow as measured by arterial spin labeling, gait kinetics, impaired blood pressure variability/hemodynamic instability, bioenergetics (capacity to recover from acidosis) and many others [references to some of these studies included in the review report.]

Other relevant studies were not included because they did not report on “diagnostic testing outcomes, such as ROC/AUC, sensitivity ...”

Comment Six -- **Opinion of experts important and should be considered at this stage of development, not ruled out because of an “inherent risk of bias”. The potential for bias should be noted but work not entirely discounted as a result.** (Cross reference to Comment one dealing with case definition)

Reference in Review -- ES-29 *“Given that the condition is a syndrome with a constellation of symptoms and lacking a gold standard for diagnostic comparison, it is at inherent risk of bias by the opinion of experts.”*

Discussion – Attempts to minimize bias may inadvertently have resulted in important information being ignored or downplayed.

In spite of an attempt to undertake the review impartiality through extraction of the evidence to tables (which are then carefully compared) inconsistencies and gaps arise. Many studies trying to bridge distance between case definitions (pattern recognition) and the biological underpinnings.

Scadding JG. Diagnosis: the clinician and the computer (Ref. 117 (p. 90) Lancet. 1967;2((7521):877-82 PMID:4168324) is used as a reference for the term ‘syndrome’: *“a combination of symptoms and signs which have been observed to occur together so frequently and to be so distinctive that they constitute a recognizable clinical picture.”* The Scadding reference also discusses the natural evolution from the use of pattern recognition to one that is more rules-based [And, more amenable to the strict evidence-based medicine approach.]

The evolution noted by Scadding has been described more recently by authors Clayton Christensen, Jerome Grossman and Jason Hwang in their book, *The Innovator’s Prescription: A Disruptive Solution to Health Care*. McGraw Hill 2008. They see an evolution from *“intuitive medicine”* using and needing highly trained professionals to *“empirical medicine.”*

p. xxii *“When precise diagnosis isn’t possible, then treatment must be provided through intuitive medicine, where highly trained and expensive professionals solve medical problems through intuitive experimentation and pattern recognition. As patterns in these patients become clearer, care evolves into the realm of evidence-based, or empirical medicine – where data is amassed to show that certain ways of*

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treating patients are, on average, better than others. Only when diseases are diagnosed precisely, however, can therapy that is predictably effective for each patient be developed and standardized. We term this domain *precision medicine*.”

Comment Seven– Structured Abstract is misleading. It would be helpful if it could be rewritten so that it reflects what is in the actual document. Some specific suggestions are included below.

1. Leaves the reader with a more positive impression about the evidence and conclusions than is evident when the report is actually read ...
2. It does not accurately reflect the uncertainty that **characterizes** and permeates the findings of the review. It reports on some of the findings but it does not include some very important limitations. The effect of this omission gives a distorted view as to what the review actually found.

An example of a structured abstract that is more forthcoming on Limitations is that on Sleep Apnea .. limitations – “Very few trials evaluated objective clinical outcomes. Data were meager for many specific questions. Studies were generally of moderate to poor quality, and often had short followups, high dropout rates, and poor analyses and reporting.

Omissions Include

- i) ES 29 and p. 77 Applicability: “Several features limit its generalizability to the broader population of patients with ME/CFS, including factors surrounding the diagnosis itself.”
- ii) Insufficiency in the conclusions should include -- ES 29 and p. 77 Implications for Clinical and Policy Decisionmaking -- “*the limitations in applicability as well as the limitations of the evidence base make it difficult to draw firm conclusions with implications for clinical practice*”
- iii) They should also include --
“*Because of limitations in the evidence base, we did not have high confidence in any of the findings from this review [regarding treatment?? or all] ...*”
- iv) It would be helpful if the abstract also stated what the review did along the lines as is noted in ES-2 “*It identifies areas of future research needed to better inform the diagnostic process and treatment strategies.*”

Comment Eight – Possible Confusion about what is meant by ‘methods’

It is not explained what “methods” encompasses and indeed it appears that the way it is applied limits methods to scales, tests and tools... not history, application of case definitions, ruling out of other conditions.

*Reference in Review ES-2 p. 10 Key Question “What methods are available to clinicians to diagnose ME/CFS and how do the use of these methods vary by patient sub-groups”
Question 1 a What are widely accepted diagnostic methods and what conditions are required to be ruled out*

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ES 9 No studies evaluated a diagnostic test for ME/CFS using an adequate size and spectrum of patients and no studies demonstrated an accurate and reliable method for identifying patients or subgroups of patients with ME/CFS

The only methods that are discussed are things such as the artificial neural network test (ANN), Schedule of Fatigue and Anergia for CFS (SOFA-CFS) and the SF-36.

The CCC has a listing of conditions that should be ruled out, none of these are discussed in the review paper. The ICC excludes primary psychiatric disorders, somatoform disorder and substance abuse as well as noting the necessity of identifying and treating other diagnoses.

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Comment Nine --- Report does not even look at symptom related outcomes other than fatigue The a priori decision not to include other outcomes is ill-considered and shows a lack of understanding of the condition.

*“ES-30 “Given the breadth of symptoms in ME/CFS, we **a priori** elected to not review symptom related outcomes except for fatigue. Some interventions may have revealed benefit for other characteristics of ME/CFS and this review would not have identified these outcomes.”*

And yet, ES-31 Future Research “It is particularly important for future studies to report findings according to the cardinal features of ME/CFS such as PEM, neurocognitive status, and autonomic function as treatment choices may differ for subsets of the population”

From Discussion of ICC definition of ME “Using ‘fatigue’ as a name of a disease gives it exclusive emphasis and has been the most confusing and misused criterion. No other fatiguing disease has ‘chronic fatigue’ attached to its name – e.g. cancer/chronic fatigue, multiple sclerosis/chronic fatigue – except ME/CFS.”

Comment Ten– Exclusions

Please improve transparency regarding the reasons for excluding studies from consideration. Explain what codes 2-4 involve

There is a lack of transparency regarding exclusions – They simply note a number (as prime reason for exclusion) but it is difficult to ascertain exact reasons ... (Sleep Apnea review for instance, provides more information regarding exclusions such as why population not relevant – e.g. stroke, Alzheimer)

Examples

De Becker P, McGregor N, De Meirleir K. A definition-based analysis of symptoms in a large cohort of patients with chronic fatigue syndrome. *J Intern Med* 2001; **250**: 234–40. Exclusion code 5 -- having looked at this study, it was difficult to determine why it would have been excluded

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Also Lloyd A, Hickie I, Wakefield D, et al. A double-blind, placebo-controlled trial of intravenous immunoglobulin therapy in patients with chronic fatigue syndrome. *Am J Med.* 1990;89(5):561-8. PMID: 2146875. Exclusion code: 5

excluded code 2 -- Jason LA, Najjar N, Porter N, Reh C. Evaluating the Centers for Disease Control's empirical chronic fatigue syndrome case definition. *J Disabil Pol Studies* 2009; 20: 91-100

Comment Eleven – Exclusions continued --- **Were authors contacted if questions arose regarding studies?** -- A. From Research Protocol –*Contacting Authors: In the event that information regarding methods or results appears to be omitted from the published results of a study, or if we are aware of unpublished data, we will query the authors to obtain this information.*

Comment Twelve-- **Have the following studies been checked for relevance?**

Jason LA, Helgerson J, Torres-Harding SR, Carrico AW, Taylor RR: Variability in diagnostic criteria for chronic fatigue syndrome may result in substantial differences in patterns of symptoms and disability. *Eval Health Prof* 2003, 26: 3-22. (ME and CFS)

Jason LA, Torres-Harding SR, Jurgens A, Helgerson J. Comparing the Fukuda *et al.* Criteria and the Canadian case definition for chronic fatigue syndrome. *J. Chronic Fatigue Syndr.* 2004; **12**: 37–52.

King C, Jason LA (2004). Improving the diagnostic criteria and procedures for chronic fatigue syndrome *Biological Psychology* 68 (2005) 87–106 (Looks at CDC definitions)

Leonard A. Jason, Meredyth Evans, Molly Brown, Nicole Porter, Abigail Brown, Jessica Hunnell, Valerie Anderson, Athena Lerch (2011). Fatigue Scales and Chronic Fatigue Syndrome: Issues of Sensitivity and Specificity *Disability Studies Quarterly* (2011) Vol 31 No 1

Keller B, Pyor JL, Giloteaux L (2014) Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO2 peak indicates functional impairment *Journal of Translational Medicine* 2014, 12:104 doi:10.1186/1479-5876-12-104

Twisk FN (2014). Myalgic Encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS): The essence of objective assessment, accurate diagnosis, and acknowledging biological and clinical subgroups. *Frontiers in Physiology.* accessed on October 15 2014 at <http://journal.frontiersin.org/Journal/10.3389/fphys.2014.00109/full>

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Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is an often disabling condition with devastating effects on patients' lives and on the national economy. As noted by the Draft AHRQ Report on Diagnosis and Treatment of ME/CFS (Draft Report), more than one million Americans suffer from ME/CFS [ES-1], and, once afflicted, “most adult patients never [return] to work” [ES-2]. Not surprisingly, the economic impact of this disease is “considerable” [ES-2].

Despite the scope of this problem, there are “no medications for the treatment of ME/CFS approved by the U.S. Food and Drug Administration,” “no accepted diagnostic tests or treatments,” and not even any understanding of a “clearly identifiable etiology and disease process” [all at ES-2]. In recent years, ME/CFS research has uncovered promising findings in areas as diverse as autoimmunity, neuroinflammation, mitochondrial dysfunction, cytokine levels, viral activation, and endocrine disruption. However, annual federal funding for ME/CFS research is approximately \$5 million dollars – much lower than the norm for any other condition with a similar scope and health impact. Due to this severe and continuing shortage of funding, most ME/CFS studies are very small and designed with an eye to conserving scarce funds. The overall funding situation is so dire, the patient community has even resorted to crowd-funding to keep the pace of research moving forward.

With this background, any developments that might aid ME/CFS research are welcome. Although the patient community is sometimes viewed as hostile to government efforts related to ME/CFS, in fact we would be thrilled for any assistance in support of the many areas of critical research that are still lacking. Everyone would be pleased if this AHRQ report process really fulfilled its intention to enhance the state of ME/CFS research by summarizing in one place all the “current research on the clinical diagnosis of ME/CFS and the efficacy and harms of multiple medical and nonmedical interventions to treat ME/CFS in adults” [v]. Unfortunately, by employing questionable methods to select the evidence considered, then relying on that faulty evidence to report misleading results and conclusions, this Draft Report misstates the field it seeks to clarify. Moreover, because the AHRQ also expects that its final report “may be used ... as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies” [ii], this flawed Draft Report runs a risk of misleading the health care system at large. This misleading information could bring real harm to the million-plus ME/CFS patients in their search for medical care and for the insurance coverage to pay for it.

Like many other patients, advocates, and researchers from the ME/CFS community, I recommend that **any final report must, at a minimum, (1) remove any studies relying on the scientifically questionable Oxford definition of ME/CFS, (2) remove references to the widely discredited PACE trials, and (3) rewrite the two misleading statements of Conclusions.**

Selection of Included Studies and Problems of Exclusion

A research review like this one is best applied to a field that has been well analyzed in a large number of research studies. It is a poor fit with ME/CFS. The dismal lack of funding for

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ME/CFS research has forced researchers to design cheaper, smaller, more limited (in time and in scope) studies intended largely as pilot studies for further inquiry. These studies are frequently published in smaller journals that were not indexed for this review. At this point, researchers are still casting a wide net to figure out what's going on with the ME/CFS disease process. There have been promising studies in fields as disparate as autoimmunity, neuroinflammation, cytokine levels, mitochondrial dysfunction, viral activation, and immune dysfunction, but at this point, no consensus answers have emerged.

Because this AHRQ review process was a poor fit with the state of ME/CFS research, the Draft Report's strict inclusion standards essentially edit out the entire field of ME/CFS research. Of the 5,902 potentially relevant results in the initial resource search, only approximately *one percent* of those studies (64) were found to meet the inclusion criteria [ES-8]. Of these, only 36 were interventional trials [v]. Diagnostic efforts related to the search for biomarkers were dismissed out of hand, and research on disease etiology was, bafflingly, dismissed as unimportant to treatment. Trials of immune modulators and antivirals receive barely a mention – perhaps because any study with a treatment intervention of less than 12 weeks was automatically discarded, even though the Draft Report acknowledges that antiviral and antibiotic treatments show some promise for treating ME/CFS and “are traditionally prescribed for a shorter duration” [ES-30]. These exclusions might be acceptable if the Draft Report simply determined that the state of ME/CFS research does not currently support any clear conclusions about the Report's key questions. Instead, however, the Draft Report departs from this standard of strict inclusion to allow studies based on at least one clearly faulty definition, including one infamous study that has been discredited. The findings from this wrongly defined and poorly designed study are the *only* results to receive a mention in the Draft Report's conclusions.

Research Definitions of ME/CFS

At this time, agreeing on an acceptable case definition is one of the central challenges of ME/CFS research, diagnosis, and treatment. Without an adequately specific and widely accepted disease definition, research results may be skewed by inclusion of study subjects outside the actual patient population in question. The Draft Report catalogs eight different existing research definitions of ME/CFS and chooses to treat all of them as essentially equal. That choice dooms the results from the start because a few of the included definitions – in particular the “Oxford definition,” which requires only subjective reports of fatigue without the other standard diagnostic markers of ME/CFS – are drawn so broadly that they pull in patients who may have depression and other causes of fatigue outside the medical condition known as ME/CFS.¹ The Draft Report specifically acknowledges that the Oxford definition “has the potential of inappropriately including patients that would not otherwise be diagnosed with ME/CFS and may provide misleading results” [ES-29, emphasis added].

¹ The second Conclusions section states that “Multiple case definitions for ME/CFS exist with those that require symptoms of PEM, neurological impairment, and autonomic dysfunction representing a more severe form of the condition.” In fact, most experts agree that symptoms of PEM, neurological impairment, and autonomic dysfunction *are* the condition. Anything that doesn't involve those symptoms is medically unexplained fatigue, not ME/CFS.

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And then – despite subjecting everything else to inclusion criteria so strict that 99% of studies were discarded – it proceeds to include Oxford-based studies *anyway*.

The PACE Trial

The use of Oxford-based studies is particularly significant because it opens the door for the Draft Report to rely upon one particularly poorly designed Oxford-based study known as the PACE trial. The PACE study reported mildly promising results for cognitive behavioral therapy (CBT) and graded exercise therapy (GET) as treatments for ME/CFS. However, those findings are unreliable because of the particularly poor design of the PACE study. First, the study used the Oxford definition, which is likely to accidentally include patients with depressive disorders as a cause of fatigue. In fact, a subsequent paper reported that 46% of the PACE subjects had anxiety, depression, or both. Patients with anxiety and/or depression traditionally respond well to both CBT and GET. In contrast, for actual ME/CFS patients, GET frequently causes additional harms from post-exertional malaise (a point that is included in the Draft Report, to its credit), and the main benefits of CBT are the benefits that therapy provides to *any* patient suffering a long and disabling illness. Moreover, the PACE authors later admitted that they changed the data requirements just before analysis – patients could enter the study with an SF-36 physical function score of 65 or less, but the authors dropped their standard for “recovery” from a proposed score of 85 to a final score of 60. A patient could enter the study at 65, report a *worse* post-trial score of 60, and be reported as “recovered.”

With a questionable study population and questionable measures of recovery, there is simply no way that the PACE trial can be trusted as a reliable look at possible treatments for ME/CFS. Because the Draft Report rejected so many other studies for inadequate design, it is mind-boggling that this deeply flawed study would be declared one of the Report’s few sources of “good” results. In fact, the Draft Report itself warns that results for the CBT and GET studies “need to be interpreted with caution” given flaws in the evaluation of outcomes, over-reliance on self-reporting, and lack of measurement for activity versus inactivity [ES-28]. And then, as with the Oxford definition, the Draft Report goes on to ignore its own cautions and highlight these studies *anyway*.

¹ The second Conclusions section states that “Multiple case definitions for ME/CFS exist with those that require symptoms of PEM, neurological impairment, and autonomic dysfunction representing a more severe form of the condition.” In fact, most experts agree that symptoms of PEM, neurological impairment, and autonomic dysfunction *are* the condition. Anything that doesn’t involve those symptoms is medically unexplained fatigue, not ME/CFS.

Problems with Draft Conclusions²

² In light of a “key question” related to the potential harms of a ME/CFS diagnosis, the Draft Report states several times that a diagnosis of ME/CFS carries proven harms. The discussion correctly acknowledges that these harms can stem from prejudice in the medical community, a lack of understanding about ME/CFS, and the chronic and disabling nature of the disease

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The Draft Report specifically acknowledges problems with both the Oxford definition and the CBT and GET results. However, the two Conclusions sections inexplicably go on to highlight CBT and GET as the most [ES-80] or even the only [vi] potentially beneficial ME/CFS treatment. That is no small mistake. If this Draft Report truly lives up to its stated goal of informing health providers and insurers on the state of ME/CFS research, it will provide the entire medical community with a fundamentally inaccurate view of the field. With all the most promising research developments wiped out by the Draft Report's exclusion criteria, gone are all the studies on potential biomarkers and quantifiable physical changes. The potential promise of immune modulators and of drugs like antivirals and antibiotics receives some discussion in the Executive Summary text [see, e.g., ES-27], but potential pharmaceutical treatments receive no mention at all in the final Conclusions [pages v, 80]. Anyone using this Draft Report, as expected, to develop clinical practice guidelines or as a basis to determine reimbursement or coverage policies [see ii] will rely on the Conclusions to take away a message that only CBT and possibly GET could successfully treat ME/CFS. And so most doctors will be more than happy to continue ignoring a disease that many falsely believe is all in patients' heads, and insurers will be thrilled to have a reason to deny claims for expensive, potentially beneficial medications in favor of much cheaper therapy-based solutions. Meanwhile, a million people – most of them unable to work and many unable to even leave their homes or their beds because of this devastating illness – will continue to wait in vain for treatment.

It is because of these misleading and potentially dangerous conclusions that the patient community strongly objects to the current Draft Report. The final report must reverse its current reliance on flawed and discredited studies like the PACE trials and any other study based on the Oxford definition. Ideally, the final report also will do a better job of at least acknowledging the many promising areas of research not currently discussed in the report. At a bare minimum, the Conclusion sections must be rewritten to better reflect the serious concerns regarding CBT and GET studies as acknowledged elsewhere in the Draft Report itself.

² In light of a “key question” related to the potential harms of a ME/CFS diagnosis, the Draft Report states several times that a diagnosis of ME/CFS carries proven harms. The discussion correctly acknowledges that these harms can stem from prejudice in the medical community,

[ES-11, ES-27]. As a patient, I can confirm that, quite simply, it's stressful to lose your vitality to a severely disabling disease that your doctors can't even explain, much less fix. It's worse still when many doctors stigmatize the disease and the public at large doesn't understand it. But I genuinely don't know what to make of the statement in the Results that a “diagnosis of ME/CFS is associated with broad psychosocial consequences” [v] and in the Conclusions that “GET appears to be associated with harms in some patients whereas the negative effects of being given a diagnosis of ME/CFS appear to be more universal” [vi, ES-80]. I don't understand the logical connections in those sentences well enough even to suggest a correction. The negative effects of a ME/CFS diagnosis come from the lack of hope for treatment and improvement – directly from the lack of good research as reflected in this Draft Report – not from some quality inherent in the diagnosis itself.

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a lack of understanding about ME/CFS, and the chronic and disabling nature of the disease [ES-11, ES-27]. As a patient, I can confirm that, quite simply, it's stressful to lose your vitality to a severely disabling disease that your doctors can't even explain, much less fix. It's worse still when many doctors stigmatize the disease and the public at large doesn't understand it. But I genuinely don't know what to make of the statement in the Results that a "diagnosis of ME/CFS is associated with broad psychosocial consequences" [v] and in the Conclusions that "GET appears to be associated with harms in some patients whereas the negative effects of being given a diagnosis of ME/CFS appear to be more universal" [vi, ES-80]. I don't understand the logical connections in those sentences well enough even to suggest a correction. The negative effects of a ME/CFS diagnosis come from the lack of hope for treatment and improvement – directly from the lack of good research as reflected in this Draft Report – not from some quality inherent in the diagnosis itself.

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To: Scientific Resource Center
Portland VA Research Foundation
Subject: Comments on AHRQ Draft Comparative Effectiveness Review
Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
Date: October 18, 2014

Attached are comments on the Evidence Review conducted by AHRQ on the *Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)*.

The attached comments reflect significant concerns with how this Evidence Review has been conducted, the diagnostic, subgroup and treatment conclusions drawn by this report and the risk of undue harm that this report creates for patients with myalgic encephalomyelitis (ME). A final version should not be published until these scientific issues are resolved.

Most fundamentally, this Evidence Review is grounded in the flawed assumption that eight CFS and ME definitions all represent the same group of patients that are appropriately studied and treated as a single entity or group of closely related entities. Guided by that assumption, this Evidence Review draws conclusions on subgroups, diagnostics, treatments and harms for all CFS and ME patients based on studies done in any of these eight definitions. In doing so, the Evidence Review disregards its own concerns as well as the substantial body of evidence that these definitions do not all represent the same disease and that the ME definitions are associated with distinguishing biological pathologies. It is unscientific, illogical and creates undue risk of harm to lump disparate patients together without regard to substantive differences in their underlying conditions.

Compounding this flawed assumption are the *a priori* choices in the Review Protocol that ignored critical questions and instead focused on a narrowly defined set of questions and applied restrictive inclusion and exclusion criteria. As a result, evidence that would have refuted these flawed starting assumptions or that was required to accurately answer the questions was never considered. Some examples of how these assumptions and protocol choices negatively impacted this Evidence Review include:

- Evidence about the significant differences in patient populations and in the unreliability and inaccuracy of some of these definitions was ignored and/or dismissed.
- Diagnostic methods were assessed without first establishing a valid reference standard.
- Critical biomarker and cardiopulmonary studies, some of which are in clinical use today, were ignored because they were judged to be etiological studies or used the wrong statistics, regardless of the importance of the data.
- Treatment outcomes associated with all symptoms except for fatigue were disregarded, potentially resulting in a slanted view of treatment effectiveness and harm.
- Treatment trials that were shorter than 12 weeks were excluded, even if the treatment duration was therapeutically appropriate.
- Counseling and CBT treatment trials were inappropriately pooled without regard for the vast differences in therapeutic intent across these trials.
- Conclusions about treatment effect and harms failed to consider what is known biologically about ME and patients likely response to the therapies that are being recommended.
- The Evidence Review states that its findings are applicable to all patients meeting any CFS or ME definition regardless of the case definition used in a particular study.

The issues with this Evidence Review are substantial in number, magnitude and extent. At its root is the assumption that any case definition is as good as the rest, and that studies done on one patient population are applicable to every other patient population, despite the significant and objective differences among these patients. The failure to differentiate between patients with the symptom of

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subjective unexplained fatigue on the one hand, and objective immunological, neurological and metabolic dysfunction on the other, calls into question the entire Evidence Review and all conclusions made about diagnostic methods, the nature of this disease and its subgroups, the benefits and harms of treatment and the future directions for research.

As the Evidence Review states, the final version of this Evidence Review may be used in the development of clinical practice guidelines or as a basis for reimbursement and coverage policies. It will also be used in the P2P workshop and in driving NIH's research strategy. Given the likelihood of those uses and the Evidence Review's claim of broad applicability to all CFS and ME patients, the flaws within this report create an undue risk of significant harm to patients with myalgic encephalomyelitis and will likely confound research for years to come. These issues, more fully outlined in the attached comments, must be addressed before this Evidence Review is issued in its final form.

Signed:

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To: Scientific Resource Center, Portland VA Research Foundation
From: Mary Dimmock, et al.
Subject: Comments on AHRQ Draft Comparative Effectiveness Review
Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue
Syndrome
Date: October 18, 2014

These comments are the first of a two part set of comments on the Evidence Review that discuss the following topics:

1. The issues with the Evidence Review's base assumption that all CFS and ME definitions represent the same disease or set of closely related diseases;
2. The analysis and conclusions drawn regarding diagnostic methods, accuracy and concordance of definitions, subgroups and diagnostic harms;
3. The analysis and conclusions drawn regarding treatment effects and harms; and
4. Applicability, reliability and future research directions

This section deals with the first two of these topics. It is understood that the Evidence Review did not include any questions asking if CFS and ME differ or not. Instead, the Evidence Review assumes that all definitions represent the same disease or closely related diseases and considers them to be a valid clinical entity. Because of this, the Evidence Review may consider the comments on this issue to be out of scope for this review. However, it is scientifically unreasonable and unethical to make recommendations about diagnostics, treatments and harms in one patient population based on studies done in another patient population. Given the evidence that these definitions do not encompass the same populations, this Evidence Review must reassess the validity of its core assumption and the conclusions made on the basis of that assumption.

KEY FINDINGS

1. The Evidence Review must discuss the substantial evidence that refutes its assumptions that the eight CFS and ME definitions represent the same or closely related disease(s) and that that disease is a valid clinical entity linked together by medically unexplained fatigue.
2. In light of that evidence, the Evidence Review must reevaluate the conclusions made about definition accuracy and concordance, diagnostic methods, subgroups, treatments and harms. It must also reevaluate its statements about the limitations and applicability of the Evidence Review findings.
3. The Evidence Review needs to reconsider the impact of Evidence Review criteria that unduly excluded critical evidence about diagnostics and subgroups and reevaluate the conclusions made about diagnostics, subgroups and treatments in light of those excluded studies. Examples of the excluded evidence that needs to be reconsidered includes:
 - a. Objective biomarker and exercise diagnostics (e.g. CPET, NK Cell function, tilt table test, CPET);
 - b. Studies objectively demonstrating subgroups; and
 - c. The DePaul Symptom Questionnaire
4. The Evidence Review needs to consider not only the harm but also the benefit of a diagnosis. More importantly, the Evidence Review must clearly acknowledge the harm done to ME

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patients when psychological theories and treatments are applied to a disease with demonstrated organic pathologies.

The Evidence Review comments listed below also highlight a number of errors in content and in the application of the stated inclusion and exclusion criteria, which inappropriately excluded studies. The full set of recommendations is included in the attached comments.

Explanation on terminology used in these comments

The Evidence Review includes eight definitions that use the labels “CFS,” “ME/CFS,” or “ME,” and states that for this Evidence Review, the terms will be used synonymously. (p. ES-1) However, there is a disease characterized by post-exertional malaise [PEM] and associated with neurological, immunological, autonomic, and energy production impairment that has historically been referred to as ME. The most recent case definition, the 2011 Myalgic Encephalomyelitis International Consensus Criteria (ME-ICC) specifically advocates that patients meeting ME criteria be removed from the category of “CFS.”

To be clear on what is being referred to, going forward, this document uses the term “ME” to refer to the disease described by the ME-ICC and the 2003 Canadian Consensus Criteria. (CCC) The term “CFS” is used to refer to the 1991 Oxford Definition, the 1994 Fukuda Definition or the 2005 Reeves Definition and to the broader condition of unexplained fatigue described by this Evidence Review.

1. The Evidence Review’s assumption that eight definitions all encompass the same disease/set of closely related diseases is unproven and unscientific and calls into question all conclusions made by this Evidence Review

1. The Evidence Review is based on the assumption that eight separate CFS and ME case definitions are equivalent representations of the same disease or group of related diseases.
2. This assumption of equivalency fails to account for evidence demonstrating this to be a faulty assumption:
 - a. Significant and irreconcilable differences in definition inclusion and exclusion criteria
 - b. Evidence of diagnostic unreliability and irreproducibility of CFS definitions
 - c. Demonstrated biological distinctiveness and importance of hallmark criteria
 - d. Significant differences in prevalence rates
 - e. Incompatibility of disease theories associated with CFS and ME
3. The failure to demonstrate equivalency of these definitions calls into question the entire Evidence Review and all resultant conclusions made about subgroups, diagnostic methods and treatments.

Faulty Assumption of Equivalency of Definitions as “Medically Unexplained Chronic Fatigue”

As originally defined by the P2P Working Group, the key questions to be considered by this Evidence Review included a set of questions on whether and how ME and CFS differ and whether they lie along a continuum of severity or are entirely distinct.ⁱ These questions were not included in the Evidence Review protocol, apparently because it was decided a priori that the evidence base could not answer these questions.ⁱⁱ As a result of this decision, the Evidence Review assumes that all CFS and ME definitions are equivalent descriptions of the same disease or set of closely related diseases.

The Evidence Review acknowledges the controversies “on the underlying etiology and whether the conditions represented by [the terms “ME” and “CFS”] reflect a single pathologically discrete syndrome, subsets of the same illness, or a nonspecific condition shared by other disease entities.”

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(p. ES-1) But the Evidence Review then ignores the implications of that statement and proceeds with the assumption that the eight definitions are equivalent ways of diagnosing the disease under consideration and distinguishing it from other fatiguing conditions:

“Currently diagnosing a patient with ME/CFS relies on the use of a set of clinical criteria ([eight] case definitions) to distinguish ME/CFS from other conditions that may also present with fatigue.” (p. ES-1)

Stunningly, the Evidence Review appears to suggest that the differences across definitions are a simple terminology issue and not reflective of substantive differences in the definitions themselves or the identified patient populations.

“For this review, ME and CFS will be used synonymously (ME/CFS) and will include the populations(s) studied under either of these terms, recognizing that issues regarding terminology are currently unresolved.” (p. ES-1)

In declaring these definitions to be equivalent and equally valid references for the disease being investigated, the Evidence Review focuses on *“persistent fatigue not attributable to a known underlying medical condition”* as the core feature that ties these definitions together with other symptoms being optional. (p. ES-1) Further demonstrating this focus on fatigue, the inclusion criteria for the key question on diagnosis is *“fatigue but without another underlying diagnosis”* (Appendix B-1) and the Evidence Review has chosen *“to not review symptom related outcomes except for fatigue.”* (p. ES-30)

Substantial Evidence Refutes the Evidence Review’s Assumption of Definition Equivalency

The Evidence Review fails to prove the validity of the assumption that the eight CFS and ME definitions represent the same disease or group of closely related diseases centered around *“medically unexplained chronic fatigue.”* But more importantly, the Evidence Review ignores the substantial evidence in the literature that demonstrates this assumption to be false. This evidence includes the following:

1. Significant and Irreconcilable Differences in Definition Inclusion and Exclusion Criteria

These eight definitions demonstrate significant and irreconcilable differences in inclusion and exclusion criteria. Oxford requires only 6 months of medically unexplained debilitating chronic fatigue, which Oxford itself states is subjective. Oxford is essentially unspecified chronic fatigue. Fukuda and 2005 Reeves are somewhat more restrictive, requiring unexplained fatigue plus any 4 of 8 common symptoms but the criteria are polythetic; neither Fukuda or 2005 Reeves require hallmark criteria such as PEM, in which all symptoms are exacerbated following even trivial physical or cognitive activity. Oxford, Fukuda and 2005 Reeves exclude only selected types of primary psychiatric illness (e.g. schizophrenia, bipolar illness, MDD with psychotic features) but not all types and do not recognize any diagnostic biomarkers or other objective tests.

By contrast, the ME International Consensus Criteria (ME-ICC) and the CCC both require PEM and also require neurological, immunological and other multi-system dysfunction. Neither ME-ICC nor CCC allows the inclusion of primary psychiatric illness. The ME-ICC does not even require fatigue and not all ME patients experience fatigue as a major symptom if they live within the strict energy limits imposed by the disease. Together, these facts call into question the use of fatigue as a unifying symptom. Further contrasting with Oxford, Fukuda and Reeves, both ME-ICC and CCC use objective tests in diagnosis.

Dr. Leonard Jason has demonstrated that such differences in inclusion and exclusion criteria (particularly the failure to require PEM and the inclusion of primary psychiatric illness) combined with the choice of patient characterization methods could encompass diverse illnesses,

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particularly psychiatric disorders, within a CFS diagnosis.ⁱⁱⁱ In a 2008 study of the 2005 Reeves criteria, Jason discussed the 10-fold increase in prevalence seen in 2005 Reeves over earlier definitions and demonstrated that 38% of patients with major depressive disorder were misdiagnosed as having CFS.^{iv} Dr. Jason's conclusion was that the 2005 Reeves criteria had "sensitivity and specificity problems".^v

The Evidence Review does acknowledge that "different case definitions introduce variability in the characteristics of the population identified as having ME/CFS and that some of the case definitions will be more inclusive (including patients with overlapping conditions) whereas others may be more specific." (ES-29) And the Evidence Review explicitly references Oxford as including patients who do not have "ME/CFS." (p. ES-29)

But the Evidence Review shows no evidence that it fully considered the implications of these noted differences in inclusion criteria, particularly in the requirement for hallmark criteria like PEM. Further, the Evidence Review does not appear to have considered the differences in exclusion criteria across definitions. The only discussion in either the body or the appendix was that conclusion that no study has defined strategies for evaluating exclusionary conditions. (p. 14) But this fails to address the fact that the stated differences in exclusion of psychiatric illness could easily result in substantially different patient populations. The Evidence Review needs to discuss the implications of these exclusion differences and re-evaluate its subgroup, diagnostic and treatment conclusions in light of them.

One note: In addition to the eight definitions, the Evidence Review accepts variants of these definitions. One example is the Prins' study, which used Fukuda "except for the requirement of 4/8 additional symptoms to be present." (p. G4-43) It's impossible to know what the resultant patient cohort was but it is clearly no longer a Fukuda cohort. The Evidence Review needs to reexamine the studies that used such variants of definitions and determine whether the studies should be excluded as the wrong population.

Finally, although the Evidence Review notes that Oxford could include patients who do not have the disease, the Evidence Review fails to explicitly note that the issues that plague Oxford - overly broad, fatigue-focused inclusion criteria, failure to require hallmark symptoms like PEM, failure to exclude primary psychiatric illness and the choice of tools and methods used to assess these criteria – also plague the Fukuda and 2005 Reeves definitions. The Evidence Review needs to include this evidence of lack of reproducibility and concordance and acknowledge that 2005 Reeves and Fukuda have the same limitations as Oxford.

Two notes: First, in its description of the ME-ICC definition, the Evidence Review includes statements about energy production/ transportation impairments" in the column titled "fatigue". This is not correct. The ME-ICC does not require fatigue and the energy production/transport impairments noted in the ME-ICC are not the same thing as fatigue. Secondly, the Evidence Review states that the ME-ICC recommends that the terms "CFS" and "ME" be embraced as synonymous. (p. ES-1) This is also not true. The ME-ICC discusses the problems with the non-specificity of the overly broad CFS and calls for ME to be separated from the broader CFS. Both of these issues need to be corrected.

2. Direct Evidence of Diagnostic Unreliability and Irreproducibility of CFS Definitions

The Evidence Review states that there are "no studies that quantitatively compared the diagnostic concordance of two case definitions." (p. ES-26) This is not true. The CDC conducted two studies that examined the accuracy of Fukuda; one of these also examined the concordance of Fukuda and 2005 Reeves. These studies were not included in the Evidence Review because

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they didn't address an Evidence Review question, were the wrong study type or didn't meet the Evidence Review's inclusion criteria. The first study is the CDC 2003 Wichita study that followed CFS patients from 1997 to 2000.^{vi} Of the sixty diagnosed with CFS *at some point* during the study, only 21% were still classified as CFS at the 2 and 3 year follow-up and only 7.5% maintained a CFS classification two years in a row.^{vii} The CDC 2005 Reeves study reexamined 227 subjects from the 2003 Wichita study, including 58 diagnosed with CFS at some point in the original study.^{viii} Two years after the original study, only about 13% of patients originally diagnosed with CFS were still diagnosed with CFS *using the same CFS criteria* as that used in the original study. Further, when using both the Wichita Fukuda CFS criteria and the 2005 Reeves criteria at the same time, only 25% of the patients were diagnosed as having CFS by both criteria, demonstrating an extremely low concordance.

The 2005 Reeves study acknowledges the "minimal association between the [Reeves] empirical classification and classification by the surveillance [Fukuda] criteria," and blames this on the fluctuating nature of the illness and the diagnostic approaches used in the Wichita study. But what is particularly problematic about these explanations is that studies have demonstrated that only 10% or less of ME patients recover^{ix} and the degree of remission experienced by patients is not sufficient to result in ME patients no longer retaining the diagnosis of ME.

The 2005 Reeves study demonstrates that a) Fukuda and 2005 Reeves definitions do not encompass the same group of patients and b) even in the hands of the CDC, Fukuda does not demonstrate acceptable diagnostic accuracy or reproducibility over time. Dr. Reeves emphasized this point about Fukuda, stating, "it is difficult to assess the validity of [Fukuda study] diagnostic criteria and essentially impossible to compare results between studies critically."^x

Together with Jason's study on the lack of sensitivity and specificity in the 2005 Reeves definition noted above, this is substantial evidence that both Fukuda and 2005 Reeves have problems with diagnostic reliability.

One note: The Evidence Review states that the 2005 Reeves definition "follows Fukuda, 1994 criteria, meant to define how to apply criteria." (p. Appendix I-5) But the issues raised above indicate that that is not the case. The description of the 2005 Reeves definition in the body and the appendix needs to be revised to accurately reflect the differences between the Fukuda and 2005 Reeves definitions.

3. Demonstrated Biological Distinctiveness and Importance of Hallmark Criteria

Cardiopulmonary exercise test (CPET) is the gold standard for functional capacity testing, is widely endorsed by a number of medical societies and its performance, particularly its reproducibility upon repeat test, is demonstrated in a number of chronic diseases. Using CPET on two consecutive days, Drs. Snell, Stevens, Keller, Vermeulen and others have shown that post-exertional malaise is associated with impairment in energy metabolism and lowered anaerobic threshold, worsened on the second day.^{xi} Dr. Keller stated that the findings seen with CPET demonstrate "obvious physiological anomalies in the ME/CFS response to exercise stress" and that the CPET response seen in these patients, with its characteristic 2nd day worsening of response, was distinguishable from patients with other chronic diseases or from those who are deconditioned and might respond positively to exercise.^{xii} Further highlighting the underlying biological differences associated with PEM, Dr. Newton has demonstrated a "compromised skeletal muscle response to exercise" that was associated with an increase in levels of acid in muscle and "impaired cardiac energetics."^{xiii} Drs. Kathleen and Alan Light have demonstrated differences in exercise-induced gene expression between patients and healthy controls^{xiv} and

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have also demonstrated differences in the expression of fatigue-related genes in a study that compared these patients to patients with cancer-related fatigue.^{xv}

PEM (PENE) is just one of the hallmark criteria required by the ME-ICC and the CCC; the studies demonstrates objective evidence for the neurological and immunological dysfunctions noted in ME-ICC and CCC as well. But even when looking at just PEM, the evidence of distinctive biological pathology combined with the fact that cancer-related fatigue and ME show different patterns of expression of fatigue-related genes seen in the Lights' study call into question the scientific validity of treating all medically unexplained chronic fatigue as the same clinical entity or lumping ME with the Oxford/Fukuda defined CFS in which hallmark criteria like PEM are not required.

4. Significant Differences in Prevalence Rates

Prevalence rates are widely variant across CFS and ME definitions with the highest prevalence associated with Oxford, Fukuda and Reeves. In 1997, Wessely estimated the Fukuda prevalence rate at 2.6%^{xvi} while Jason's 1999 study estimated the Fukuda prevalence rate at 0.42%.^{xvii} In 2003, CDC estimated Fukuda CFS prevalence at 0.24%^{xviii} and then in 2005, estimated a 10-fold increase to a prevalence of 2.54% using the 2005 Reeves criteria.^{xix} One study examined prevalence using both Fukuda and the Canadian Consensus Criteria (CCC) and estimated CCC prevalence at 0.11%, roughly one half of that estimated for Fukuda.^{xx} Even when the diagnosis is made by clinical assessment and the same definition is used, there are significant differences in resultant prevalence rates that reflect differences in the patient selection approaches used, an issue examined extensively by Jason.^{xxi}

Alone, these differences in prevalence estimates do not prove that ME is not a subgroup of CFS; other factors like the differences in underlying biological pathologies and differences in inclusion and exclusion criteria do prove that. But what these differences in prevalence estimates clearly demonstrate is the point that Jason made; the researchers who use different definitions and different patient selection methods are not selecting the same cohort of patients.

One note: A casual reader of the Evidence Review might be left with the impression that the lack of concordance in prevalence rates is the result of self-report versus clinical assessment. (p. ES-2) That does account for some of the variance in estimates of prevalence rates but the major source of the lack of concordance is the difference in patient populations due to differences in case definition and patient selection methods used. To avoid misunderstanding, the Evidence Review should explicitly include this fact.

5. Incompatibility of Disease Theories Associated with CFS and ME

There are two basic types of disease theories promulgated about the etiology and persistence of "ME/CFS" over time. One theory, often referred to as the "fear avoidance" theory of CFS, postulates that the disease is maintained by psychosocial factors, specifically that the patient has maladaptive beliefs about being ill and has avoided activity which resulted in deconditioning.^{xxii} Grounded in this theory, treatment by CBT and GET are intended to get patients to address their illness beliefs and reverse activity avoidance and deconditioning. Such psychosocial theories are prevalent in Oxford and sometimes Fukuda studies. Given the non-specific focus on fatigue in these definitions, each of these could select patients who would respond to CBT and GET.

The other type of disease theory is biological dysfunction, potentially caused by an ongoing infection, an autoimmune reaction, or dysregulated neurological/immunological systems - dysfunctions that are essential components of the CCC and the ME-ICC. The treatments associated with proponents of these theories include antivirals, immune-modulators, Ampligen and Rituxan; Ampligen and Rituxan have both demonstrated efficacy in clinical trials.

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It is difficult to imagine that a disease that responds to drugs like Ampligen or Rituxan is also going to respond to psychological and behavioral treatments intended to reverse the patient's maladaptive avoidance of activity and deconditioning. The Evidence Review must explain how it reconciles lumping patients who suffer from false illness belief together with patients who suffer from dysfunction in neurological, immunological and energy production systems. The current Evidence Review does not provide that explanation.

Evidence Review Conclusions Invalidated by Assumption of Definition Equivalency

This Evidence Review bases its conclusions about subgroups, diagnosis and treatment on the unproven assumption that all eight definitions represent the same or closely related disease(s), joined together by "medically unexplained chronic fatigue."

But the evidence cited above refutes the assumption at the heart of this Evidence Review.

Further, both logic and that body of evidence suggests that "medically unexplained chronic fatigue" is not a stable, reliable or scientifically valid basis for a clinical entity. Doctors do not lump migraines and arthritis together simply because they both cause pain. Similarly, Oxford CFS and CCC ME should not be grouped together because of fatigue. Logic suggests that a clinical entity organized around unexplained chronic fatigue is too non-specific and too reliant on the state of current medical knowledge (e.g. what can or cannot be explained) to be clinically meaningful and scientifically valid.

Regarding Fukuda, the Evidence Review includes Brurberg's recommendation that Fukuda be adopted as the single definition (ES-26) and that "patients should be classified according to their severity and symptom patterns." (p. 77) Those recommendations ignore the evidence, noted above, of Fukuda's unreliability and the fact that Fukuda is so broad as to embrace any number of fatiguing conditions, including psychiatric conditions, with no proof that they share a common pathology. Those recommendations also ignore the importance of an objective biomarker to address the unreliability of patterns of common symptoms. But most importantly, those recommendations ignore the fact that Fukuda does not require the hallmark criteria of the disease. ***The difference between Fukuda CFS patients with PEM and Fukuda CFS patients without PEM is not a quantitative difference in disease severity but a qualitative difference resulting from the distinctive pathology underlying hallmark criteria like PEM.*** The Evidence Review should reconsider the inclusion of these recommendations unless it discusses the factors weighing against such a recommendation.

The failure of this Evidence Review to consider this evidence or to assess the validity of its assumption that all eight definitions represent the same or closely related disease(s), joined together by "medically unexplained chronic fatigue" is startling. This faulty foundation calls into question the entire Evidence Review and all conclusions made about subgroups, diagnostics, and treatments, especially when those conclusions are claimed to apply to the entire population of people that meet any CFS and ME definition.

The Evidence Review must discuss the substantial evidence that refutes its assumptions that the eight CFS and ME definitions represent the same disease or closely related diseases and that that disease(s) is a valid clinical entity centered around medically unexplained fatigue. In light of that evidence, the Evidence Review must also reevaluate its diagnostic, subgroup, treatment and harms conclusions and its statements about the limitations and applicability of the Evidence Review findings. Finally, the Evidence Review needs to acknowledge that Fukuda and Reeves have the same diagnostic limitations as Oxford.

To protect ME patients from erroneously derived conclusions on treatment and harms, the Evidence Review must address these issues before it publishes its final report.

2. The Evidence Review's failure to establish a diagnostic reference and its narrow inclusion and exclusion criteria have resulted in invalid conclusions on definition accuracy, diagnostic methods, subgroups, treatments and harms.

- a. Fails to establish a diagnostic reference standard
- b. Fails to consider evidence of lack of definition accuracy and concordance
- c. Evaluation of diagnostic methods misses key studies and ignores definitional differences
- d. Excludes critical exercise and biomarker evidence
- e. Fails to consider differences in definition exclusion criteria
- f. Harms analysis is incomplete and slanted

Fails to Establish a Diagnostic Reference standard

Best practice for the systematic review of diagnostic standards requires the use of a diagnostic gold standard as reference, but no such diagnostic gold standard exists for either CFS or ME, a fact that "poses significant challenges for the evaluation of diagnosis tests." (p. ES-26) In its place, the Evidence Review uses any of eight case definitions as a reference, (p. 1,4) even though the Review acknowledges that different case definitions introduce variability in symptoms experienced and will include people who do not have "ME/CFS". (p. ES-29) The Evidence Review also states that no studies evaluated the accuracy of diagnostic methods (p. ES-10) or compared the concordance of two case definitions. (p. ES-26)

Because the Evidence Review was unable to summarize the strength of evidence for the diagnostic methods, (p. 60) the Evidence Review states that study quality was assessed in part based on whether the reference standard [any of 8 definitions] was "interpreted independently from the test under evaluation." (p. ES-5) The Evidence Review also states "case definitions were reviewed to interpret studies that defined populations according to different definitions." (p. 4) But the Evidence Review does not discuss how it assessed the accuracy of the underlying definitions to ensure their utility as a reference.

Fails to Consider Evidence of Lack of Definition Accuracy and Concordance

Given the foundational importance of the validity of each of the definitions as reference standards, the Evidence Review's failure to explain how it assessed the underlying accuracy of those references is a serious problem. But more importantly, the Evidence Review has failed to consider significant evidence that would have shown that some of these definitions are not accurate or concordant with each other. This is a critical oversight given the Evidence Review's noted intent to assess the reference standard independently from the test.

One such study is the 2005 Reeves paper,^{xxiii} referenced in the diagnostic methods section but excluded from the accuracy and concordance analysis because it was the "wrong study design for key question." (p. D-49) As noted above, this study demonstrates the irreproducibility of a Fukuda CFS diagnosis in the same patients over time and also demonstrates only a 25% concordance between the Fukuda and 2005 Reeves definitions. A second excluded study, discussed above, is Jason's 2008 study of the 2005 Reeves definition,^{xxiv} which demonstrated that 2005 Reeves included a significant percent of patients with primary mood disorders. Finally, Jason's 2010 paper, which was included in the diagnostic methods section but not in the accuracy and concordance section, concluded that 2005 Reeves definition had "sensitivity and specificity problems" and that only 65% of true CFS cases would be identified by the 2005 Reeves definition.^{xxv} Neither of these points was

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mentioned in the Diagnostic Methods section or the Concordance and Accuracy section but should be.

Excluded studies examining misdiagnosis of CFS further bolster the view that these definitions lack diagnostic accuracy.^{xxvi} Two studies each showed roughly 40% of patients given a Fukuda CFS diagnosis were later found to not have CFS, largely because exclusionary conditions were missed. A study of multiple sclerosis found that some MS patients were first diagnosed with CFS. These studies highlight a core problem with the risk of misdiagnosis in those CFS definitions that do not require hallmark criteria like PEM and only specifically require fatigue plus the exclusion of other conditions.

As discussed more extensively in the beginning of these comments, prevalence studies, the evidence of biological pathologies and the irreconcilable differences in disease theories also speak to the lack of concordance and accuracy of these definitions.

Collectively, the differences in inclusion/exclusion criteria and disease theory along with the studies on definition accuracy and concordance, prevalence and underlying biological pathologies call into question both the underlying assumptions of this Evidence Review and its resultant conclusions. The Evidence Review needs to include the Jason and Reeves studies in the accuracy and concordance section and explicitly acknowledge the evidence of inaccuracy and irreproducibility demonstrated in both Fukuda and the 2005 Reeves definitions. Further, the Evidence Review needs to reassess its conclusions about diagnostics, concordance, subgroups, treatments, harms and applicability in light of the breadth of this evidence.

One note on the Aslakson study^{xxvii} included in the concordance section: Based on the title, this study appears to be a 2005 Reeves definition study. Given the issues noted above and the fact that the 2005 Reeves definition has been discredited outside of CDC, the Evidence Review should reevaluate any conclusions drawn on the basis of 2005 Reeves studies.

To its credit, the Evidence Review has included 6 studies examining definition concordance although it failed to include at least 12 other similar studies for a variety of reasons.^{xxviii} Based on the 6 studies that were reviewed, the Evidence Review correctly states that patients identified by the CCC or the ME-ICC have more severe symptoms, greater functional impairment and differences in objective biomarkers than those seen in patients identified by the CFS criteria. (p. ES-10, 17) The Evidence Review calls for future studies to report findings according to hallmark criteria such as “PEM, neurocognitive status and autonomic function.” (p. ES-31)

But the Evidence Review then concludes that patients that meet the ME-ICC and the CCC “appear to represent a more severe *subset* of the broader ME/CFS population.” (p. v - emphasis added) As written, this statement and other similar statements in the Evidence Review endorse the concept of a broader “CFS” as a valid clinical entity in which patients meeting the ME-ICC and the CCC are a subgroup. But there is an alternative interpretation in which patients who meet the ME-ICC and CCC represent a separate and distinct clinical entity. This alternative position is broadly supported by the fundamental differences in the inclusion and exclusion criteria of these definitions and the distinctiveness of hallmark criteria like PEM, suggesting not just *quantitative* differences in the level of severity but *qualitative* differences in the underlying biological pathologies.

The Evidence Review does not demonstrate scientific validity of the broader CFS population as a clinical entity, especially when that entity is centered on medically unexplained chronic fatigue. Unless the Evidence Review does so, it should avoid making statements that endorse its validity and ME’s position as a subgroup in it.

One note on the Van Hoof study examined in the concordance analysis: the Evidence Review states

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that “ME subjects had lower functioning than CFS subjects on the role-emotional and mental health subscales of the SF-36.” This is incorrect. Van Hoof’s paper states that CFS patients scored lower on these scales. (p. 17)^{xxix}

Evaluation of Diagnostic Methods Missed Key Studies and Ignored Definitional Differences

The Evidence Review included 11 diagnostic studies of which 7 were focused on symptoms and symptom scales (e.g. SF-36, MFI-20) and 4 on biomarkers. In analyzing diagnostic methods, the Evidence Review focuses solely on the accuracy of the given diagnostic method itself as it applies to a given definition. The assessment of diagnostic methods ignores evidence of the lack of accuracy of the underlying definition and the resultant implications for the validity of the diagnostic method or its applicability across all CFS and ME case definitions.

For instance, the Evidence Review rated an Oxford CFS study of an artificial neural network as “good” but failed to explain the relevance of the study to patients meeting ME-ICC or CCC or consider its own statement that Oxford includes those who do not have the disease. (p. 13) Further, the rating of ‘good’ is questionable since a good rating has “clearly described the population” (p. 6), something that the Evidence Review acknowledges is a problem with Oxford. (p. ES-29)

Another example is the review of the 2010 and 2011 diagnostic methods studies by Jason.^{xxx, xxxi} Both of these studies examined the 2005 Reeves definition and the 2010 paper specifically described sensitivity and specificity problems as noted above. But in both cases, the Evidence Review focuses its discussion on the accuracy of the diagnostic methods used (e.g. SF-36, the CDC Inventory, MFI-20) and fails to discuss Jason’s conclusion about the unreliability of the 2005 Reeves definition (p. 12) or Reeves conclusions about the lack of reproducibility of Fukuda. This is a remarkable omission, given that this information is germane to an assessment of the quality of each definition as a valid reference standard.

Surprisingly, the Evidence Review does not include the DePaul Symptom Questionnaire (DSQ) as a diagnostic method. The DSQ, evaluated in at least three studies,^{xxxii} was developed to specifically assess both the Fukuda and Canadian criteria. This addresses a fundamental shortcoming in many of the tools examined in this Evidence Review, like the MFI and SF-36, which according to Jason, are “general purpose diagnostic tests”^{xxxiii} that do not target the specific symptoms of CFS and thus select overly broad populations. Unlike other diagnostic methods, DSQ specifically targets hallmark criteria like PEM and uses not only the presence but also the severity and frequency of symptoms to achieve required sensitivity and specificity. Jason has demonstrated the validity of the DSQ in 3 different patient populations (two U.S. and one U.K) and has also confirmed that post-exertional malaise and neurocognitive impairments must be present for a diagnosis. Finally, one of these studies evaluated a machine learning method that when combined with DSQ, provided an accurate method of diagnosing patients who experience ME’s hallmark symptoms. The Evidence Review should include DSQ in its evaluation of symptom-based diagnostic methods. It should also acknowledge the critical importance of requiring hallmark criteria like PEM and of assessing severity and frequency of symptoms, not just the presence of symptoms.

One note: this Evidence Review included Jason’s “Energy Envelope” study, (p. 13) as a diagnostic method. This study assessed the relationship between symptom patterns, coping strategies and whether patients stay in their “energy envelope.” It does not appear to be evaluating a diagnostic method for CFS or ME.

Excludes Critical Exercise and Biomarker Evidence

The Evidence Review correctly notes that the “utility of symptom-based scales in differentiating

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patients with this disease remains inconclusive.” (p. 18) Ultimately, patterns of common symptoms are not the solution to the diagnostic challenges of ME. Objective biomarkers are. A significant body of evidence relevant to the assessment of both diagnostic methods and subgroups has not been considered because the Evidence Review’s inclusion and exclusion criteria exclude etiological studies (p. ES-25, 74) or studies that do not use the specific diagnostic outcome measures required by the Evidence Review. The rationale for excluding the etiological studies was that their “intent” was not to identify tests that “could distinguish patients who would respond to treatment.” (p. ES-25) An exclusionary criteria grounded on “intent” versus data is subjective. Further, this exclusion assumes that the only valid diagnostic tests always demonstrate which patients will respond to treatments, an assumption that is not true.

Sometimes, these studies were excluded for inexplicable reasons. Bou-Holaigah’s study on *The relationship between neurally mediated hypotension and the chronic fatigue syndrome* was excluded because of inadequate duration, even though a 12-week duration was not necessary for the study’s objective to compare tilt table tests in patients and healthy controls.^{xxxiv} But regardless of the reason for exclusion, these choices unduly limit the Evidence Review, a fact that the Evidence Review itself acknowledges at least with regards to the diagnostic outcomes exclusion. (p. ES-30)

The Evidence Review does include two CPET studies in the Diagnostic Methods section and states “CPET test capacity was significantly different between ME/CFS patients and non-disabled sedentary controls.” (p. 13) However, in each case, the Evidence Review focused its assessment only on the diagnostic utility of symptoms or symptom scales like SF-36 and MFI-20. (p.13) Remarkably, in neither case did the Evidence Review discuss the diagnostic utility of CPET itself.

Compounding this problem, the Evidence Review excludes all the other studies on cardiopulmonary exercise testing (CPET) for a variety of reasons.^{xxxv} For instance, the Evidence Review excludes Snell’s *Discriminative validity of metabolic and workload measurements for identifying people with chronic fatigue syndrome*,^{xxxvi} because it “does not address a Key Question or meet inclusion criteria.” (appendix D-1, D-56) But Snell’s paper specifically discusses the diagnostic utility of the two-day CPET, demonstrating a 95% classification accuracy. As a group, these excluded CPET studies objectively measure the energy metabolism impairment underlying PEM, using a gold standard method broadly endorsed by numerous medical societies and used across diseases. In contrast to the Evidence Review’s statement that cardiopulmonary tests were not adequately tested in a broad spectrum of patients, (p. 74) Dr. Keller has stated that the response to CPET is known in a number of chronic diseases and the response to CPET seen in ME is distinctive.^{xxxvii} The exclusion of these studies is a serious problem.

In addition, the Evidence Review also excludes a large number of other biomarker studies,^{xxxviii} most notably those for NK-cell function, tilt table tests and other autonomic measures, oxidative stress, viral load tests, plasma neuropeptide and cognitive tests. Like the cardiopulmonary exercise tests, these tests appear to have been excluded because they failed to meet the Evidence Review’s diagnostic methods outcome criteria or because the Evidence Review determined that the study’s “intent” was as an etiological study, not a diagnostic methods study. (p. 74) This body of evidence includes methods that are in use clinically today, both by disease experts and in some cases, by experts outside of this disease as in the case of tilt table tests and CPET. The exclusion of these studies is a serious flaw of this Evidence Review and its conclusions and must be addressed.

The Evidence Review’s narrowly defined inclusion and exclusion criteria affect not only the assessment of diagnostic methods but also analysis of subgroups. The Evidence Review acknowledges that “studies identified subgroups on the basis of exercise testing, cerebral blood flow as measured by arterial spin labeling, gait kinetics, impaired blood pressure variability/hemodynamic

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instability, bioenergetics (capacity to recover from acidosis), and many others.” (p. 74) But in spite of this, the Evidence Review excludes them because they do not report diagnostic testing outcomes. This demonstrates a significant flaw in the approach adopted by this Evidence Review in which it attempted to deduce subgroups of the disease through the narrow lens of a limited set of symptom based diagnostic methods studies, ignoring the substantial evidence of disease abnormalities and findings about subgroups. The Evidence Review should incorporate references to the findings of these studies in its conclusions about subgroups and include a statement about the limitations of the selected approach.

Given how few diagnostic studies met the narrow inclusion criteria used by the Evidence Review and given the importance of objective diagnostic markers to overcome the limitations of symptom based diagnosis, the choice of inclusion and exclusion criteria made by Evidence Review unreasonably excludes critical evidence on diagnostic methods and subgroups. If these studies had been included, the Evidence Review would have likely reached different conclusions not only about diagnosis but also about subgroups, treatments and harms. The Evidence Review needs to reconsider the exclusion of these studies and reassess all of its conclusions in the light of these excluded studies, particularly the CPET, autonomic and NK-cell function studies and those studies that examine subgroups.

Fails to Consider Differences in Definition Exclusion Criteria

One of the Evidence Review questions is, “What conditions are required to be ruled out or excluded before assigning a diagnosis of ME/CFS” and concludes that no studies “compared strategies for ruling out alternative diagnoses.” (p. 14) However, the Evidence Review does not appear to have conducted its own evaluation of the substantial differences in exclusionary criteria. Such differences, particularly those in psychiatric illness exclusion criteria, have important implications for the assessment of the concordance of definitions, the utility of the definitions as references and the cross-definition applicability of conclusions being made about diagnostic methods, treatments and harms. The Evidence Review needs to discuss these differences and then reassess the implications for treatment benefits and harms and the applicability of the Evidence Review findings in light of those differences.

Harms Analysis is Incomplete and Slanted

The Evidence Review correctly acknowledges the harm and stigma that patients face. However, the Evidence Review incorrectly links this harm to *getting* the diagnosis. (p. ES-11, ES-25) This is not correct. Patients often report experiencing significant relief in finally getting a diagnosis. The harm is not due to the diagnosis itself but rather to inappropriate, harmful and stigmatizing treatment by the medical community. But because the Evidence Review did not also ask about the benefits of a diagnosis, it reaches the wrong conclusion about the harms and stigma associated with getting the diagnosis. The Evidence Review needs to convey both perspectives to avoid the risk that doctors will be unwilling to give an appropriate diagnosis. Further, this should be noted as a limitation of this Evidence Review.

As noted above, the Evidence Review also fails to discuss the harm that comes to patients with other treatable diseases who are first misdiagnosed with CFS. This is a significant risk with any overly broad definition with unclear disease boundaries as is seen in Oxford and Fukuda. This broader risk of harm to other patients needs to be noted.

Finally, the Evidence Review correctly points out that patients “had a greater risk of receiving a psychiatric diagnosis” (p. ES-26) and as evidence pointed to a study of Oxford CFS patients in which 46% had been diagnosed with a psychiatric illness. The Asbring study reported that patients “experience distress from being psychologicalized by others, especially doctors.” (G3-1) But the

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Evidence Review fails to connect the dots between those facts and the promotion of the “fear avoidance” theory of CFS, in which CFS is the result of maladaptive activity avoidance and deconditioning that should be treated with GET and CBT. The promotion of such untested and unproven theories for all “ME/CFS” patients causes significant emotional and physical harm to those patients who experience the kinds of organic pathologies encompassed by the ME-ICC and CCC definitions. The Evidence Review must explicitly address this issue and clearly acknowledge the harms done to ME patients when psychological theories and treatments are applied to a disease with demonstrated organic pathologies.

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<http://www.iom.edu/~media/Files/Activity%20Files/Disease/ME/CFS/Maier%20IOM%20ME/CFS%20Presentation.pdf>
- a. How do ME and CFS differ?
- Do these illnesses lie along the same continuum of severity or are they entirely separate with common symptoms?
 - What makes them different, what makes them the same?
 - What is lacking in each case definition – do the non-overlapping elements of each case definition identify a subset of the illness or do they encompass the entirety of the population?
- ¹ According to a discussion at the June 2014 CFSAC, these questions were apparently removed from the P2P evidence review protocol because there is “not enough evidence” in the literature to consider this question.
<http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac-minutes-june-17-2014.pdf> page 38
- ¹ Jason has a substantial body of evidence on this issue. Two of the articles include
- Jason, L., Richman, J., Friedberg, F., Wagner, L., Taylor, R., Jordan, K. Politics science and the emergence of a new disease. September 1997, *American Psychologist*. Vol. 52, No. 9, 973-983 (Exclusion code: not given)
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To: Scientific Resource Center
Portland VA Research Foundation
Subject: Comments on the AHRQ Evidence Review
Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
Date: October 18, 2014

Attached are comments on the Evidence Review conducted by AHRQ on the *Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)*.

The attached comments reflect significant concerns with how this Evidence Review has been conducted, the diagnostic, subgroup and treatment conclusions drawn by this report and the risk of undue harm that this report creates for patients with myalgic encephalomyelitis (ME). A final version should not be published until these scientific issues are resolved.

Most fundamentally, this Evidence Review is grounded in the flawed assumption that eight CFS and ME definitions all represent the same group of patients that are appropriately studied and treated as a single entity or group of closely related entities. Guided by that assumption, this Evidence Review draws conclusions on subgroups, diagnostics, treatments and harms for all CFS and ME patients based on studies done in any of these eight definitions. In doing so, the Evidence Review disregards its own concerns as well as the substantial body of evidence that these definitions do not all represent the same disease and that the ME definitions are associated with distinguishing biological pathologies. It is unscientific, illogical and creates undue risk of harm to lump disparate patients together without regard to substantive differences in their underlying conditions.

Compounding this flawed assumption are the *a priori* choices in the Review Protocol that ignored critical questions and instead focused on a narrowly defined set of questions and applied restrictive inclusion and exclusion criteria. As a result, evidence that would have refuted these flawed starting assumptions or that was required to accurately answer the questions was never considered. Some examples of how these assumptions and protocol choices negatively impacted this Evidence Review include:

- Evidence about the significant differences in patient populations and in the unreliability and inaccuracy of some of these definitions was ignored and/or dismissed.
- Diagnostic methods were assessed without first establishing a valid reference standard.
- Critical biomarker and cardiopulmonary studies, some of which are in clinical use today, were ignored because they were judged to be etiological studies or used the wrong statistics, regardless of the importance of the data.
- Treatment outcomes associated with all symptoms except for fatigue were disregarded, potentially resulting in a slanted view of treatment effectiveness and harm.
- Treatment trials that were shorter than 12 weeks were excluded, even if the treatment duration was therapeutically appropriate.
- Counseling and CBT treatment trials were inappropriately pooled without regard for the vast differences in therapeutic intent across these trials.
- Conclusions about treatment effect and harms failed to consider what is known biologically about ME and patients likely response to the therapies that are being recommended.
- The Evidence Review states that its findings are applicable to all patients meeting any CFS or ME definition regardless of the case definition used in a particular study.

The issues with this Evidence Review are substantial in number, magnitude and extent. At its root is the assumption that any case definition is as good as the rest, and that studies done on one patient population are applicable to every other patient population, despite the significant and objective differences among these patients. The failure to differentiate between patients with the symptom of subjective unexplained fatigue on the one hand, and objective immunological, neurological and metabolic dysfunction on the other, calls into question the entire Evidence Review and all conclusions

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made about diagnostic methods, the nature of this disease and its subgroups, the benefits and harms of treatment and the future directions for research.

As the Evidence Review states, the final version of this Evidence Review may be used in the development of clinical practice guidelines or as a basis for reimbursement and coverage policies. It will also be used in the P2P workshop and in driving NIH's research strategy. Given the likelihood of those uses and the Evidence Review's claim of broad applicability to all CFS and ME patients, the flaws within this report create an undue risk of significant harm to patients with myalgic encephalomyelitis and will likely confound research for years to come. These issues, more fully outlined in the attached comments, must be addressed before this Evidence Review is issued in its final form.

Signed:

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To: Scientific Resource Center, Portland VA Research Foundation
Re: Comments on AHRQ Draft Comparative Effectiveness Review
Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
Date: October 18, 2014

KEY FINDINGS

- The Evidence Review’s assessment of treatments is flawed because both patient populations and treatments were inappropriately pooled.
 - The Evidence Review ignored its own concerns about overly broad definitions. *Section 1(a)*.
 - The Evidence Review ignored important differences between treatments. *Sections 1(b)-(c)*.
- The Evidence Review’s assessment of treatments incorporated multiple errors that, if corrected, could change the Review’s conclusions.
 - The Evidence Review inappropriately excluded many treatment trials based on duration and selected outcomes. *Sections 2(a)-(b)*.
 - The Evidence Review overstated the applicability of “Good” quality studies, and failed to examine the deficiencies in the PACE trial. *Sections 2(c)-(d)*.
- The Evidence Review ignored or minimized the substantial data on GET and CBT treatment harms. *Section 3*.
- The Evidence Review sections on limitations, applicability and directions for future research are incomplete and must be revised. *Section 4*.

A note on terminology: The Evidence Review included eight definitions that use the labels “CFS,” “ME/CFS,” or “ME,” and stated that for this Evidence Review, the terms were used synonymously. (p. ES-1) However, there is a disease characterized by post-exertional malaise (PEM) and associated with neurological, immunological, autonomic, and energy production impairment that has historically been referred to as ME.

The most recent case definition, the 2011 Myalgic Encephalomyelitis International Consensus Criteria (ME-ICC), specifically advocates that patients meeting ME criteria be removed from the category of “CFS.” To be clear on what is being referred to herein, these comments on the Evidence Review use the term “ME” to refer to the disease described by the ME-ICC and the 2003 Canadian Consensus Criteria (CCC). The term “CFS” is used to refer to the 1991 Oxford definition, 1994 Fukuda definition and the 2005 Reeves definition, and to the broader condition of unexplained fatigue described by this Evidence Review.

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1. The Evidence Review's assessment of treatments is flawed because both patient populations and treatments were inappropriately pooled.

- a. The Evidence Review ignored its own concerns about overly broad definitions.
- b. The Evidence Review ignored the disease theories underlying treatment trials.
- c. The Evidence Review ignored important differences among pooled psychological treatments.

1(a). The Evidence Review ignored its own concerns about overly broad definitions.

The Evidence Review explicitly stated that it used the terms ME and CFS synonymously, and included populations studied under either term and encompassing eight case definitions. (p. 1) These different case criteria were assumed to represent a single disease entity when there is no objective, physiological proof of this. While not identifying preference for one case definition over another, the Evidence Review did acknowledge that the different case definitions select different patient populations.

First, the Evidence Review acknowledged that the Oxford definition could produce misleading results because it includes people without ME/CFS:

We elected to include trials using any pre-defined case definition but recognize that some of the earlier criteria, in particular the Oxford (Sharpe, 1991) criteria, could include patients with 6 months of unexplained fatigue and no other features of ME/CFS. This has the potential of inappropriately including patients that would not otherwise be diagnosed with ME/CFS and may provide misleading results. (p. 77)

Second, the Evidence Review acknowledged that it could not draw firm conclusions about implications for clinical practice, in part because of the variability of the case definitions:

Studies surrounding aspects of diagnosis suggest that different case definitions introduce variability in the characteristics of the population identified as having ME/CFS and that some of the case definitions will be more inclusive (including patients with overlapping conditions) whereas others may be more specific but identify more severe forms of the condition albeit a smaller population. (p. 77-78)

After acknowledging the heterogeneity of the case definitions and the likelihood that Oxford studies include patients without ME, the Evidence Review then proceeded to ignore the problem.

Specifically, the Evidence Review pooled all treatment study results regardless of the case definitions used in the studies. This is remarkable for two reasons. First, the Evidence Review did not pool diagnostic studies precisely because of differences in methods, case definitions and heterogeneity of outcomes. (p. 7) Second, the Evidence Review asserted that there are no reliable diagnostic tools or methods, which calls into doubt the application of these case criteria and diagnostic methods in treatment studies. (p. 80)

The effect of case definition and patient selection on treatment outcomes can be seen in Figure 3, a meta-analysis of mean changes in SF-36 physical function subscale scores for CBT and controls. (p. 32) The highest mean changes were reported by studies using the Oxford definition.^{xxxix, xl, xli, xlii} This result is predictable given the high percentage of patients

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with psychological disorders included in these studies (see section 2(d) below), and the end result is a distortion of the data and misapplication of conclusions to patients with ME.

It should also be noted that the use of the Oxford definition was not distributed evenly across interventions. Medication and alternative medicine trials used the Oxford definition infrequently (1/9 and 2/7, respectively). In contrast, exercise and combination trials relied heavily on the Oxford definition (3/6 and 3/5, respectively). (Appendix G4) Because the Evidence Review did not distinguish among the case definitions, the true effect of this disproportionate use of Oxford in some types of trials was not examined.

The Evidence Review erred first in treating all case definitions as equivalent, despite the admitted danger of including patients who do not have ME. The Evidence Review erred again in viewing all treatment trials as applicable across case definitions without regard for the patient populations used in those studies. This effect is exaggerated in the exercise and combination studies, which relied on the Oxford definition disproportionately to the medication studies. The Evidence Review should test and report its analysis for the effects that case definition had on treatment outcomes.

1(b). The Evidence Review ignored the disease theories underlying treatment trials.

The theory of disease is an important factor in comparing and evaluating treatments. The Evidence Review noted that most patients report using treatments that target underlying causes of disease and/or specific symptoms. (p. 2) However, the Evidence Review erred in not considering the significant impact that theory of disease has on the use and applicability of different treatments.

Medication trials, in particular, focus on treating the underlying physiological pathology of ME, including infections and immune dysfunction. In contrast, the rationale for CBT and GET treatments rests on hypothetical false illness beliefs and consequential deconditioning.⁴ Fear of engaging in activity and avoidance of activity are viewed as the perpetuating factors of CFS. This “fear avoidance theory” persists in the face of studies demonstrating that there is no exercise phobia in CFS patients without comorbid psychological disorders.^{xliii}

The contradictions between these dueling causal hypotheses should be explicitly examined in the Evidence Review. Common sense dictates that a disease caused by a pathogen or immune dysfunction will not be successfully treated by therapy aimed at correcting false illness beliefs, and vice versa.

To claim that correcting patients’ false illness beliefs could adequately treat multiple sclerosis or hypothyroidism would be malpractice and quackery. Similarly, a disease like ME characterized by multisystem dysfunctions and measurable physiological abnormalities cannot be credibly treated by convincing patients that they erroneously believe those physiological problems to exist. The reverse is also true: patients with the single symptom of chronic fatigue are not likely to respond to treatment with antivirals or immune modulators, in the absence of measurable immune dysfunction.

The failure to examine the disease theory underlying the included treatment trials increases the risk of overgeneralizing treatment effects. Medication effects should not be assumed for populations that do not match the study cohorts, and the same is true of behavioral and

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counseling effects. A treatment benefit or harm for one cohort should not be generalized to all cohorts, particularly due to the use of overly broad case definitions.

1(c). The Evidence Review ignored important differences among pooled psychological treatments.

While the Evidence Review correctly refused to pool all medication trials because each study examined a different intervention, the same principle was not applied to counseling and behavior therapies. The sixteen trials of counseling and behavior therapies actually encompassed group CBT, individual CBT, self-instruction booklets, pragmatic rehabilitation, peer-to-peer counseling, and symptom consultation. (p. 27) Yet these widely different therapeutic approaches were combined and compared to no treatment, support, relaxation, or adaptive pacing. It is hardly a surprise that this mixed bag produced only low strength evidence of benefit.

Critical differences among the counseling and behavioral therapies cannot be ignored. For example, some studies focused on support,^{xliv} stress management,^{xlv} activity management and diet,^{xlvi} or Envelope Theory and coping skills.^{xlvii} In stark contrast, other studies challenged somatic attributions,^{xlviii} activity avoidance and unhelpful beliefs,^{xlix} fatigue-related cognitions,^l precipitating and perpetuating factors,^{li} or sought to reduce perfectionism and self-criticism.^{lii}

Counseling that seeks to support and improve coping is at the opposite end of the disease theory spectrum from counseling that challenges somatic attributions, unhelpful beliefs or seeks to reduce perfectionism. Lumping these studies together, as if one type of counseling is as good or as applicable as another, introduces more heterogeneity into the analysis than already exists. Not only has the Evidence Review combined the heterogeneous patient populations, but it compounded the error by combining heterogeneous treatments within the counseling category, and then referred to all studies as CBT and counseling regardless of the study's intent or disease theory.

Medication trials were not pooled and compared because the Evidence Review correctly noted that each trial tested a different intervention, although all fell within the category of "medication." The same rigor should be applied to the counseling trials because, while all the studies fall within the category of "counseling," the interventions tested are so heterogeneous that they cannot be pooled and analyzed.

2. The Evidence Review's assessment of treatments incorporated multiple errors that, if corrected, could change the Review's conclusions.

- a. The Evidence Review inappropriately excluded many treatment trials based on an erroneous view of duration.
- b. The *a priori* decisions on treatment outcomes prejudiced the analysis.
- c. The treatment studies accorded a "Good" quality assessment rating cannot be assumed to be applicable to all patients.
- d. The Evidence Review failed to examine and report the deficiencies in the PACE trial.

2(a). The Evidence Review inappropriately excluded many treatment trials based on an erroneous view of duration.

The Evidence Review required a minimum duration of twelve weeks for intervention studies in order to account for the relapsing-remitting nature of ME. (p. 5) However, this requirement

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focused on the intervention duration, as opposed to follow-up, and it biased the results away from shorter acting interventions.

The twelve-week timing criterion for treatments was applied to the length of time an intervention was used and not the length of time the subjects were studied. This led to the exclusion of studies such as a trial of rituximab to treat CFS.^{liii} (Appendix D-19) However, this study actually followed the subjects for twelve *months*, noting a delayed response to the treatment. Furthermore, the dosing schedules for rituximab vary by indication, but in no indication is the drug approved for continuous administration for twelve weeks.^{liv} It is nonsense to exclude a twelve-month study because the intervention was not administered for twelve weeks, particularly when the intervention in question is not used that way.

Other intervention trials were excluded for using a duration of less than twelve weeks. For example, a study of hyperbaric oxygen therapy was excluded because fifteen treatments were administered over three weeks.^{lv} (Appendix D-2) Similarly, a study of the MAO inhibitor selegiline was excluded because the trial was six weeks in length, as was a trial of phenelzine.^{lvi,lvii} (Appendix D-41) Both studies showed a positive effect in the treatment group, and the phenelzine study explicitly hypothesized that treatment benefit would be swift.

As a direct result of the twelve-week requirement, the Evidence Review ignored interventions that are intended for shorter use or that can show a swift benefit. It is possible that inclusion of these studies may have changed the Evidence Review's conclusions. Exclusion of these studies may also have biased the Evidence Review toward including more behavioral and exercise intervention studies, and fewer medication trials.

It is true that ME can have a relapsing-remitting pattern, and the Evidence Review correctly recommended that intervention trials use follow-up periods of greater than one year to determine effectiveness over time. (p. 79) However, a distinction should be made between length of active treatment and the length of follow-up. It is detrimental to patients to focus on treatments that must be administered continuously for long periods of time, when short-acting treatments may be of benefit.

A total of fifty-six studies were excluded from the Evidence Review based on duration. The Evidence Review acknowledged the risk that the duration requirement may have biased results, but only in the context of antiviral and antibiotic therapies. (p. 78) This view is too narrow. Many other medication trials were excluded because the interventions were not continuously administered for twelve weeks. The duration requirement and the way it was applied (focusing on intervention length, not follow-up) creates a significant limitation on the applicability of the Evidence Review's conclusions on treatment.

2(b). The *a priori* decisions on treatment outcomes prejudiced the analysis.

The Evidence Review made several *a priori* decisions on treatment outcomes that biased the analysis of treatment studies:

We considered outcomes of overall improvement, fatigue, function, quality of life, and employment which we considered clinically significant and conducive to the systematic review methodology. Given the breadth of symptoms in ME/CFS, we *a priori* elected to not review symptom related outcomes except for fatigue. Some

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interventions may have revealed benefit for other characteristics of ME/CFS and this review would not have identified these outcomes. (p. 78)

By focusing on symptom related outcomes for fatigue alone, the Evidence Review excluded consideration of post-exertional malaise – one of several symptoms that the Evidence Review noted were hallmark characteristics of the disease. (p. 1) No justification was offered for the decision to ignore these hallmark characteristics in assessing treatment benefit, and the Evidence Review should account for this inconsistency.

Furthermore, the outcome measures for treatments that were included in the Evidence Review are almost exclusively self-report measures. (Appendix J-16 to J-19) Of the twenty outcomes measures listed, none were validated to the CCC or ME-ICC and fourteen were not validated to any CFS case definitions whatsoever. The lack of validation of these measures should be noted as a serious limitation of the evidence base.

Very few studies reported objective physical function outcomes, although this is clearly one of the most important outcomes for assessing treatment benefit. Appendix G4 identifies only four studies that included objective measures of functional capacity^{lviii,lix,lx, lxi} The PACE trial's results on the six-minute walking test are not reported in this Evidence Review. This is inexplicable given that those results were the only objective measurement of the purported therapeutic target of physical conditioning. Failure to consider objective outcome measures such as actigraphy data also excluded evidence that neither GET nor CBT produced increased overall activity levels.^{lxii, lxiii}

A total of eighty-one studies were excluded from the Evidence Review for using the wrong outcomes. A number of these studies were treatment trials using self-reported outcomes or objective outcomes such as antibody titers and cardiac function^{lxiv, lxv, lxvi, lxvii, lxviii} Inclusion of studies like these may have altered the Evidence Review analysis of treatments.

The *a priori* decision to focus on self-report measures and changes in fatigue (as opposed to other ME symptoms) narrowed the scope of the Evidence Review. Including studies that used changes in physiological measures like antibody titers would have broadened the number of interventions examined by the Review. Examining data on objective measures of physical function like activity would have not only broadened the evidence base, but would have introduced data that call into question the assessment of GET benefits. There is no question that the selection of outcomes measures ultimately changed the Evidence Review's conclusions, and the Evidence Review must explicitly acknowledge the detrimental impact of those *a priori* decisions.

2(c). The treatment studies accorded a “Good” quality assessment rating cannot be assumed to be applicable to all patients.

Of the thirty-six intervention trials evaluated in the Evidence Review, only six received a “Good” quality rating. (Appendix H2) One study tested an alternative medicine intervention.^{lxix} Four studies tested CBT or counseling therapies.^{14,9,13,3} One study was a combination trial.⁴ The quality ratings clearly contributed to the “Moderate” strength of evidence assessment for CBT's reduction of fatigue and global improvement (p. 66), and GET's improvement of overall function (p. 69) and global improvement. (p. 70) However, these conclusions must be interpreted with great caution because of the significant differences among these studies.

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First, as discussed in section 1(c), there are notable differences in the therapeutic approaches of the CBT/counseling studies. For example, one study tested envelope theory and coping skills,⁹ while another focused on strategies to reduce perfectionism.¹⁴ These vastly different studies might individually meet the criteria for a “Good” rating, but should not be combined to assess strength of evidence.

Second, the patient populations studied in these six “Good” trials are vastly different from one another, and very different from ME patients. Two of the studies used the Fukuda criteria, and both ruled out psychiatric illness.^{9,13} Three studies used the Oxford criteria^{14,3,4} and a fourth used Fukuda or Oxford.³¹ Exclusions applied for mental illness varied among these studies, as well. One study excluded those with severe depression;¹⁴ another did not.³ Another study only excluded those who were at significant risk of self-harm,⁴ while another did not use any exclusion for psychological disorders at all.³¹

The Evidence Review combined different CBT/counseling modalities, different case definitions, different exclusions applied to a single case definition, and different case ascertainment methods. These studies are rated “Good,” and then included as support for “Moderate” strength of evidence in several categories. The differences among these studies begs the question of whether the combined strength of evidence can be as high as “Moderate.” The Evidence Review should refine its assessment in order to account for the risk that these disparate study designs produced results that are not applicable to even a majority of ME patients.

2(d). The Evidence Review failed to examine and report the deficiencies in the PACE trial.

The PACE trial featured prominently in this Evidence Review.⁴ It is the largest of all the intervention trials examined, and it reported significant improvement on several outcome measures. However, the Evidence Review failed to examine any of the well-documented deficiencies in this study, which if considered would likely downgrade the Review’s assessment of the trial.

First, the Evidence Review failed to connect its concerns about the Oxford definition (p. 77) with the subject selection criteria for PACE. The PACE authors used the Oxford definition, and excluded patients “at significant risk of self-harm.”⁴ While Oxford requires the exclusion of patients with psychosis, bipolar disorder, substance abuse, and organic brain disorder, it does not require the exclusion of patients with depressive or anxiety disorders. Indeed, a subsequent paper reported that 46% of the PACE subjects had anxiety, depression or both.^{lxx} Another paper examined the patients enrolled from one PACE center and found that 56% of subjects had a co-morbid psychiatric disorder, including depression, anxiety, obsessive compulsive disorder, post-traumatic stress disorder, and phobias.^{lxxi}

The CBT and GET programs tested in the PACE trial would be predicted to benefit patients with primary psychiatric disorders. Whether the PACE treatments would benefit an ME cohort without co-morbid psychiatric disorders is an important and unresolved question. In addition, the inclusion of patients without ME through the use of the Oxford definition calls into question whether the PACE results can be generalized to ME patients even if they have secondary depression or anxiety. Therefore, the applicability of the PACE results to patients with ME cannot be assumed.

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Second, PACE relied heavily on self-report outcomes measures, and even discarded the original plan to measure subject activity through actigraphy.^{lxxii} In a follow-up paper, inexplicably excluded from the Evidence Review, the PACE authors acknowledge that objective measures do not correlate well with self-report measures.^{lxxiii} The objective measure reported in the PACE trial is the six minute walking test, with the biggest improvement reported in the GET arm of the trial (an increase of 67 meters over baseline to 379 meters).⁴ However, the PACE authors fail to note that this improvement still left the subjects below the 400 meter threshold qualifying for lung transplantation.^{lxxiv} The PACE authors have defended the poor results, pointing to variations from how the test is usually performed.^{lxxv} However, the fact remains that the improvements, even in the GET arm, were not remarkable and not indicative of gain of function.

Third, the follow-up paper on recovery in the PACE trial revealed several *post hoc* changes to data analysis.³⁵ The most startling is the definition of recovery with an SF-36 physical function score of 60 or less (reduced from the original threshold of 85 or less).³⁴ Given that the entry criteria for PACE included an SF-36 score of 65 or less, this change permits the outcome of patients being classified as “recovered” when in fact their physical function decreased from baseline. This threshold is also notable because the 2005 Reeves Empirical definition uses a diagnostic threshold of 70 or less on the same scale.^{lxxvi} Finally, PACE data show that there was a slight increase in the number of participants receiving illness and disability benefits by the end of the trial.^{lxxvii}

Fourth, the PACE subjects were enrolled based on meeting the Oxford criteria, but were also assessed with the “international criteria” for CFS and the London criteria.⁴ It must be pointed out that the international criteria referenced by the authors was Reeves 2003,^{lxxviii} and that the four symptoms required to accompany fatigue were only required to be present for *one week*.³⁵ There is also some controversy over whether the proper London criteria was used.^{lxxix} The authors report that 67% of PACE participants met the modified CDC definition, and 51% met the London criteria.³⁵ However, these assessments were made on the Oxford cohort, not independent cohorts, and therefore it is difficult to draw conclusions about patients meeting other case definitions (including correctly applied Fukuda and London).

The PACE trial results and subsequent publications have been very controversial. The Evidence Review did not include several of the follow-up papers, and assigned a “Good” quality rating without acknowledging or addressing the many flaws of the PACE trial: PACE used an overly broad definition that could include people with other causes of fatigue; almost 50% of PACE subjects had psychiatric disorders; objective measures of physical function showed minor or no improvement; recovery was redefined in such a way that patients who worsened from baseline could be counted as recovered; and application of additional diagnostic criteria was flawed.

Given these significant flaws, there is a danger of overstating the results of PACE, and certainly a high risk in drawing conclusions about whether PACE is applicable to ME patients. The Evidence Review should reexamine the PACE data, and reconsider its quality assessment. Furthermore, the Evidence Review should interpret the PACE results with caution, particularly the strength of evidence assessments that include PACE.

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3. The Evidence Review ignored or minimized the data on treatment harms.

- a. The Evidence Review ignored substantial evidence of harms associated with GET.
- b. The Evidence Review's finding of no harms associated with CBT is flawed.

3(a). The Evidence Review ignored substantial evidence of harms associated with GET.

In studying the evidence of harms associated with exercise trials, the Evidence Review noted that harms were not well reported overall and that the evidence was insufficient (p. 21), although "GET appears to be associated with harms in some patients." (p. 80) This statement underplayed not only the caveats noted within the Evidence Review itself, but completely ignored evidence that would explain and confirm the harm signal noted by the Review.

The Evidence Review noted that GET was associated with a higher number of harms and withdrawals in several trials. (p. 60) In addition, the Review stated that, "the limited and vague reporting of harms in many studies may suggest outcome reporting bias for these outcomes." (p. 79) Finally, "the high rate of patients refusing repeated exercise testing in one study due to concern of harm suggests that this outcome has not been adequately studied." (p. 49)

There are substantial data that explain the higher rates of harms noted in GET trials, most of which was ignored by this Review. Many studies have documented physiologically abnormal responses to exercise in ME patients, including muscle dysfunction,^{lxxx} oxidative stress,^{lxxxii} gene expression,^{lxxxiii} and cardiopulmonary function.^{lxxxiii,lxxxiv,lxxxv} The Evidence Review excluded most of these studies through its misguided *a priori* decision to exclude studies that were "intended" to identify etiology. (p. 74)

This "strong evidence of impaired physiological responses to exercise" explains why "incautiously applied GET is likely to result in exacerbation of fatigue and other symptoms of ME/CFS patients."⁴⁷ This is precisely what ME patients have reported regarding exercise for years, both in patient surveys and at the FDA Patient Focused Drug Development Initiative.^{lxxxvi,lxxxvii,lxxxviii} The Evidence Review ignored the fact that a trial of CBT and GET found an increase in SF-36 pain scores at follow-up in the intervention group.^{lxxxix} The Review also failed to examine a systematic review that reported increased harms associated with GET.⁴⁹

The Evidence Review first cast its net broadly, including studies using the Oxford definition despite the fact that these studies included patients without "ME/CFS." (p. 77) Then the Evidence Review acknowledged that "harms may differ between patient subgroups" and that the failure to conduct subgroup analysis in trials may have missed this effect. (p. 77) It concluded, "Clearly reporting harms particularly surrounding exercise testing and treatment for specific subgroups may help identify patients more negatively affected by these interventions." (p. 80)

The Evidence Review failed to connect the dots. Half of the exercise studies used the Oxford definition, and one study was larger than the rest of the trials combined. (Table 5) Oxford studies included patients who did not have ME. Harms in these trials were inadequately reported, although there is a signal that GET was more harmful than other treatments. Ample evidence in the literature shows that ME patients have demonstrable, abnormal physiological responses to exercise that would lead to an exacerbation of PEM and associated harms.

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The Evidence Review's call for more subgroup analysis is sensible, but it underplays the serious risk of harm for ME patients who are prescribed exercise. An adequate examination of the literature would support this conclusion. The Evidence Review should modify its conclusion that "GET *appears* to be associated with harms in *some* patients" (p. 80, emphasis added) to accurately reflect the data.

3(b). The Evidence Review's finding of no harms associated with CBT is flawed.

As with the studies on GET, the Evidence Review overstated its conclusions that there are no harms associated with CBT. The Review acknowledged that "Harms of counseling and behavioral therapies were poorly reported but there is low strength of evidence that counseling is not associated with harms based on one moderate-sized trial." (p. 21) The trial referred to in this statement is the PACE trial.

Some of the multiple flaws of the PACE trial are more thoroughly examined in section 2(d) above. In summary, PACE used the Oxford definition and therefore included patients without ME, as the Evidence Review noted. PACE subjects had high rates of psychological disorders, and the CBT arm was based on the "fear avoidance theory" of disease that results in deconditioning. This theory holds that CFS is "reversible and that cognitive responses (fear of engaging in activity) and behavioural responses (avoidance of activity)" are responsible for the perpetuation of the condition.⁴ The therapeutic intent is to correct the patients' maladaptive fears and behaviors that are keeping them ill.

It is quite possible that such an approach would be helpful to some of the Oxford patients, particularly those suffering from primary depression, anxiety, and obsessive compulsive disorder. However, it is clear from the data that patients who have an organic disease characterized by neurological, immunological and metabolic impairments would not have a meaningful therapeutic response and would be at higher risk for harm. Furthermore, a systematic review found that in nine pooled patient surveys, 20% of patients reported harms from CBT.⁴⁸

The Evidence Review criticized the counseling and CBT trials for failing to conduct subgroup analysis to detect harms in subgroups of patients, but then disregarded these concerns and concluded there is low evidence that CBT is not associated with harms. Given the heterogeneity of treatment modalities included in counseling and CBT trials, and given the inclusion of patients who do not have ME, there is insufficient evidence to conclude that CBT is not associated with harms. The Evidence Review should downgrade its assessment of the strength of evidence on this point, and be more explicit about the effect of case definitions on its conclusions.

4. The Evidence Review sections on limitations, applicability and directions for future research are incomplete.

- a. There are a number of important limitations to the evidence base that were not identified in the Evidence Review.
- b. The applicability of the Evidence Review findings to real-world clinical settings is not established.
- c. The Evidence Review failed to identify several crucial needs in future research.

4(a). There are a number of important limitations to the evidence base that were not identified in the Evidence Review.

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The Evidence Review noted a number of limitations on the evidence base including: that important studies may not have been identified; that other diagnostic testing studies may provide further insight into identifying patients with ME/CFS; that treatment studies shorter than twelve weeks were not included; that outcomes for symptoms other than fatigue were not included; that published studies may have been affected by conflicts of interest or bias; and that studies were generally of poor quality. (pp. 78-79) We agree that all of these are serious limitations of this Evidence Review, and wish to add several more that should also be explicitly noted.

First and foremost, the Evidence Review assumed that CFS and ME are a single entity adequately described by any of eight case definitions (see section 1(a) above). This is an assumption and the Evidence Review is obliged to acknowledge it as such. All of the Review's conclusions about diagnostics, subgroups, treatments and harms are based on that starting presumption of equivalence. It biased the entire Review, and that must be explicitly stated.

Second, the Evidence Review failed to acknowledge that poor study quality is largely a result of the low levels of research funding available. Many studies, such as diagnostic studies using a derivation cohort, are early pilot studies. (p. 74) Small sample sizes and case-control study designs are less expensive. In addition, the multiple flaws in treatment trials – including failure to conduct more than one trial, small sample size, failure to collect data on baseline measures and harms, and lack of subgroup analysis (pp. 75-77) – are due in part to the paucity of funding. While examination of research funding levels was not an express part of this Evidence Review, it must be acknowledged as a factor affecting the evidence base. The ME evidence base cannot be properly assessed without understanding this critical limitation: niggardly research funding has restricted ME research to small pilot case-control studies, with a few larger studies looming over the landscape and potentially biasing this assessment of the field as a whole.

Third, the Evidence Review noted that some outcome measures were validated in the CFS population while others were not. (p. 76) This understates the problem. As noted in section 2(b) above and Appendix J, fourteen of twenty treatment outcomes measures were not validated to even a single ME or CFS case definition.

Fourth, as also noted in section 2(b) above, this Evidence Review focused almost exclusively on self-reported measures, and the only symptom outcome considered was fatigue. The failure to examine objective measures of function, combined with the failure to consider treatment studies that used biomarker changes such as viral titers, resulted in the exclusion of many studies. These studies would have changed the Evidence Review's conclusions about the effect of CBT and GET on function, and would have expanded the evidence on medication trials.

Finally, the Evidence Review excluded all studies examining biomarkers or physiologic tests “because the intent of these was to identify an etiology rather than understand how the specific test could distinguish patients that would respond to treatment.” (p. 74) With a single stroke, hundreds if not thousands of studies were swept from consideration. Regardless of whether this broad generalization was merited, it had the indisputable effect of narrowing the evidence base considered in this Evidence Review. Again, this limitation and its ramifications for the Review's conclusions must be expressly acknowledged.

4(b). The applicability of the Evidence Review findings to real-world clinical settings is not established.

The Evidence Review claimed that its findings are applicable to real-world clinical settings in part because they included all case definitions of “ME/CFS,” and because the interventions represented most of the commonly used treatment modalities. (p. 77) This is simply not the case.

As discussed more thoroughly in section 1(a) above, the inclusion of all case definitions in the Evidence Review actually reduced the applicability of its findings to ME patients. The Review even acknowledged that the Oxford definition “has the potential of inappropriately including patients that would not otherwise be diagnosed with ME/CFS.” (p. 77) For this reason alone, the Evidence Review’s findings are not applicable to patients with ME.

This failure of applicability is especially true for ME patients because they have documented abnormal physiologic responses to exercise. The Evidence Review did acknowledge, “Subgroup analysis in the GET trials would help in identifying if there are specific patients who might have great benefit or experience great harm.” (p. 78) However, the Evidence Review failed to discuss the data that show ME patients have significant, distinct responses to exercise in gene expression⁴⁴ and cardiopulmonary measures.⁴⁵ In fact, one paper pointed out: “data from the second CPET in this and prior studies indicate that aerobic energy-producing processes fail to respond normally to exercise stress in ME/CFS patients. Thus, incautiously applied GET is likely to result in exacerbation of fatigue and other symptoms of ME/CFS patients.”⁴⁷ The Evidence Review failed to draw the obvious connection between that data and the high rates of harms and dropouts in GET trials. Not only does this failure undercut the applicability of the Evidence Review’s conclusions, it creates a high risk that the Evidence Review will be used to perpetuate the harmful prescription of exercise to ME patients who are physically incapable of exercising without incurring harm.

The Evidence Review correctly noted, “treatment of ME/CFS often involves multiple concurrent therapies” (p. 78) but also claimed that the Review’s “interventions and comparators represented most of the therapeutic modalities commonly used in clinical practice.” (p. 77) This is not true. Treatments used for ME patients include a number of medications and therapies excluded from the review including immune modulators, beta blockers, antihypotensives, antidepressants, antivirals, antibiotics, antifungals, stimulants, pain medications, sleep medications, IV saline, and manual physical therapy. The protocol used for the Evidence Review excluded almost all of this research. The Evidence Review must explicitly acknowledge this weakness in the applicability of its findings.

Finally, the Evidence Review stated that the lack of a gold standard for diagnostic comparison creates “an inherent risk of bias by the opinion of experts,” such as the identification of PEM as a critical feature without methods for testing and monitoring the symptom. (p. 77) However, this is a very one-sided view of bias. For example, a small number of researchers hold to the “fear avoidance theory” and/or “deconditioning and exercise intolerance theories of chronic fatigue syndrome” despite evidence to the contrary in patients with ME (see sections 1 and 2 above). On the other hand, there is a growing body of evidence around PEM and how to measure its effects, as well as objective proof of the phenomenon. Competing schools of thought are to be expected in areas of scientific controversy, but bias in the face of contradictory evidence is something different. The

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Evidence Review should acknowledge the risk of bias among all experts, and also explicitly acknowledge the objective evidence that contradicts such bias.

4(c). The Evidence Review failed to identify several crucial needs in future research.

The Evidence Review identified eleven future research needs for the definition, diagnosis, and treatment of ME and CFS. (pp. 79-80) Several items require further explication, and several needs were missed.

First, the Review stated, “it would be ideal if future intervention studies consistently used an agreed upon single case definition to reduce variability in the patient samples.” (p. 79) We agree that a single case definition is needed, but it is critically important that such a definition be *accurate*. It is not simply a matter of selecting a case definition because it has been the most frequently used or because it selects the broadest group of patients.^{xc} It is time to establish a gold standard for ME, tied to the hallmark disease criteria of PEM and cognitive dysfunction, and to thoroughly research these patients. It is also time to stop applying non-ME case definitions to ME patients, as if they all belonged in the same definitional bucket.

Second, the Review recommended that the “development of a set of core outcomes . . . would help guide research and facilitate future data syntheses.” (p. 79) We agree, but the core outcomes must include objective measures. As discussed in section 2(b), objective outcomes measures must be used in order to accurately measure function. Studies could incorporate actometer data from multiple time points, as well as measurements of flexibility and cardiopulmonary function. It is of critical importance that future studies measure overall activity levels, not just compliance with an exercise or behavioral modality, as several studies have shown that subjects may reduce other activities in order to complete an exercise program.

Third, the Evidence Review omitted several key research needs. There is a dearth of natural history and longitudinal studies, and these must be pursued using an accurate ME cohort. Larger, definitive studies on diagnostic biomarkers are required. And obviously, conducting the number and types of studies required to truly advance the diagnosis and treatment of ME will require a significant increase in funding. That is the only path forward for ME patients.

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Comments on Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), AHRQ Draft Report

Abstract

The conclusions in the abstract do not match the evidence in the rest of the report and perpetuate the discredited idea that CBT and GET are the only possible approaches. This is a disservice to the community of patients with ME/CFS. For example, the conclusion of the abstract reads “*CBT and GET have shown some benefit whereas other interventions have insufficient evidence to guide clinical practice. GET appears to be associated with harms in some patients.*” This is too strong a statement given that the evidence in Table A is contradictory. CBT/counseling studies have “*mainly positive results, but mixed.*” *GET has positive results, but GET+CBT has no effect. In addition, GET studies had high withdrawals due to harms.*” In addition, on page 27 “*There is low strength evidence, based on 14 trials, that CBT, either group or individual; self-instruction booklets; pragmatic rehabilitation; peer-to-peer counseling; and symptom consultation provide improvement in fatigue, function, quality of life, and employment in adult patients with ME/CFS.*” And on page 31: “*In summary most trials of CBT or other counseling techniques suggested improvement in overall functioning and fatigue symptoms in ME/CFS patients though in a trial that followed individuals up 5 years after counseling, this affect was no longer seen.*” Finally, on page 32, Figure 3. Only three studies show a statistically significant improvement on the SF-36 scale, Deale et al. (1997) (used Oxford definition), and two by White et al. (2011) (PACE Trial, used Oxford definition). The Oxford definition is much too broad, requiring only fatigue to diagnose ME/CFS, and includes people with other fatiguing illnesses, including depression. Please revise the statements in the abstract about CBT and GET to reflect the actual findings in the report.

The conclusion of the abstract states “*...negative effects of being given a diagnosis of ME/CFS appear to be more universal.*” This seems like odd wording and gives the impression that doctors should not diagnose ME/CFS. In fact the entire “Key Question 1c. What harms are associated with diagnosing ME/CFS?” seems strange. There are many negatives associated with having a debilitating and chronic illness with no known cause, no treatment and no cure, but, in my experience, receiving the diagnosis is a relief. I have two teenagers with ME/CFS, and having a diagnosis of ME/CFS was very helpful in dealing with school authorities who, prior to the diagnosis, insisted that I was a bad parent and my kids were shirking school.

Please revise this statement in the abstract to reflect the fact that it is having the illness causes problems, not receiving the diagnosis.

Executive Summary

Page ES-1 “*Uncertainty persists regarding the etiology and whether the condition reflects a single pathologically discrete syndrome, subsets of the same illness, or a nonspecific condition shared by other disease entities.*” The end of this sentence is an old and discredited view of ME/CFS. Researchers in the field recognize that ME/CFS is a separate, organic illness. Please delete the end of this sentence.

Page ES-3 (also page 2) “*Childhood ME/CFS is uncommon...*” This is not true. Childhood ME/CFS has about the same prevalence as adult ME/CFS.

Page ES-25 (also page ES-2, page 2, page 19, page 60) “*Evidence suggests that carrying an ME/CFS diagnosis is associated with perceived stigma, financial instability, difficulty in social interactions and relationships, and a greater risk of receiving a psychiatric*

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diagnosis.” Again, it is not carrying the diagnosis that causes problems, but having a chronic illness. Please consider rephrasing this statement.

Page ES-26 (also Table 7, page 75) “*Patients with ME/CFS report feeling stigmatized by their diagnosis in terms of financial stability, work opportunities, perceived judgments on their character, social isolation, and interactions with the health care system.*” Again, it is not carrying the diagnosis that causes problems, but having a chronic illness. Please consider rephrasing this statement.

Page ES-28 “*One study comparing CBT with cognitive therapy, anaerobic exercise, or relaxation found that those patients who remained within their energy envelope (avoided overexertion and under exertion by exerting a comfortable range of energy) had a significant improvement in mean fatigue and functioning scores regardless of treatment arm.*” This is an important point and should be emphasized. In fact, this would be a better statement for the abstract than the existing and inaccurate one about CBT and GET.

Page ES-29 (also page 4, page 14, page 77): “*We elected to include trials using any pre-defined case definition but recognize that some of the earlier criteria, in particular the Oxford (Sharpe, 1991) criteria, could include patients with 6 months of unexplained fatigue and no other features of ME/CFS.*” I don’t understand this decision. If you think the Oxford definition has serious issues, then you should not give studies using it the same credence as studies using more detailed criteria. Please consider removing or down-weighting the importance of the Oxford criteria studies.

Page ES-30 “*Across all intervention trials, heterogeneity in the population samples (different case definitions used for inclusion), outcomes evaluated, and tools used to measure these outcomes, limited the ability to synthesize data. Acceptance of a single case definition and development of a core outcome set would aide in better studying the interventions to allow for more meaningful guidance for clinicians, policy makers, and patients.*” This is an important point. One thing that would help with arriving at a single case definition would be to find biological markers for ME/CFS. There is quite a bit of promising research and it is very strange that none of it was included in this review. In fact it was deliberately excluded as relating to etiology and not to diagnosis. It is too late to revise the scope of this review, but hopefully future reviews will include studies searching for biomarkers that might lead to better diagnostic criteria.

Body of the Report

The evidence presented in the body of the report about GET is contradictory, yet the conclusion in the abstract suggests that GET is helpful. Here are some quotes from the report.

Page 21: “*Graded exercise treatment (GET) was superior to control groups in measures of fatigue (low strength), function (moderate strength), and clinical global impression of change (moderate strength) based on one-good quality and three fair-quality randomized trials.*”

Page 46: “*There is low strength of evidence that exercise therapy was superior to control groups in measures of fatigue, function, and clinical impression of change.*”

Page 49 and page 76: “*In summary, GET improves function (moderate strength), and global improvement (moderate strength), and fatigue (low strength) in ME/CFS patients compared with control groups.*”

Page 76: “*Several previous studies have found worsening effects with exercise*”

Of the 4 exercise trials summarized in Figure 4 (changes in CGI scale) and Figure 5 (changes in SF-36 scale), three use the Oxford criteria -- Fulcher and White (1997) and two by White et al. (2011) (PACE Trials). This report acknowledges issues with the Oxford criteria, so it is surprising that the conclusion in the abstract relies so heavily on these studies. Please revise the abstract and executive summary to reflect the actual evidence in the report.

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Typos:

Page ES-9: “diagnostic uncertainly” should read “diagnostic uncertainty”

Page ES-26 and page 70: missing closing quotation mark on “combination of symptoms and signs which have been observed to occur together so frequently and to be so distinctive that they constitute a recognizable clinical picture.

Page 46: “serious hars” should read “serious harms”

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October 19, 2014

I am writing to request the cancellation of the AHRQ's P2P Workshop on ME/CFS and its Draft Comparative Effectiveness Review because both are rife with flaws. I believe that the P2P Workshop results will negatively affect much needed ME research, public perception of ME, and treatment by physicians for years to come. I unequivocally object to the P2P for ME/CFS for these reasons:

- ME/CFS experts have already adopted the Canadian Case Definition for research. No new definition is needed.
- The Workshop is examining the wrong illness. They are examining "medically unexplained fatigue," not Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.
- NIH has not engaged or involved stakeholders in a substantive way.
- The Workshop panel consists of non-ME/CFS experts.
- HHS has made numerous contradictory statements about the purpose of the Workshop, so its goal is unclear.
- The recent draft report, "Diagnosis and Treatment of ME/CFS," from AHRQ is inaccurate, self-contradictory, and reflects a poor understanding of ME/CFS research. AHRQ's Draft Report violates its own mission statement.*

The P2P workshop has not produced good science and sound recommendations. I hope you will give my concerns a fair hearing, and that you will cancel the P2P Workshop.

*AHRQ's mission is to improve the quality, safety, efficiency and effectiveness of health care for all Americans.

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Comments on Key question 1c: “What harms are associated with diagnosing ME/CFS?”

There are several other studies of misdiagnoses in patients diagnosed with probable or definite CFS/ME that you might want to consider (Lawn et al, 2010; Newton et al, 2010; Devasahayam et al, 2012; Brimmer et al, 2013). The latter three studies show that between 40 and 50% of patients with a provisional or definite diagnosis of CFS/ME have alternative diagnoses.

Also of relevance to the potential harm consequent upon being given a diagnosis of CFS or ME, one large primary care prospective study suggested there might be a difference in prognosis depending on which particular diagnostic label was given, although this was not a randomised study (Hamilton et al, 2007). This subject has been well reviewed by Huibers and Wessely (2006).

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Comments on the Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Draft Report

I'm deeply concerned that the many substantial flaws within this report will create an undue risk of significant harm to patients with ME and that it most likely will hamper, retard and confuse the much needed ME/CFS research for years to come. These issues must be addressed before the Evidence Review is issued in its final form.

The failure to differentiate between patients with the symptom of subjective unexplained fatigue on the one hand, and objective immunological, neurological and metabolic dysfunction on the other, calls into question the entire Review and all conclusions made about diagnostic methods, the nature of this disease and its subgroups, the benefits and harms of treatment, and the future directions for research.

Accepting eight disparate ME or CFS definitions as equivalent in spite of dramatic differences in inclusion and exclusion criteria - even contradictory/mutually exclusive in some aspects - , the Review draws conclusions on subgroups, diagnostics, treatments and harms for all CFS and ME patients based on studies done in any of these eight definitions. In doing so, the Evidence Review disregards its own concerns, as well as the substantial body of evidence that these definitions do not all represent the same disease and that the ME definitions are associated with distinguishing biological pathologies. It is unscientific, illogical and risky to lump disparate patients together without regard to substantive differences in their underlying conditions.

Compounding this flawed assumption are the a priori choices in the Review Protocol that ignored critical questions and instead focused on a narrowly defined set of questions and applied restrictive inclusion and exclusion criteria. As a result, evidence that would have refuted these flawed starting assumptions or that was required to accurately answer the questions was never considered. The Evidence Review must discuss the substantial evidence that refutes its assumptions that the eight CFS and ME definitions represent the same or closely related disease(s) and that that disease is a valid clinical entity linked together by medically unexplained fatigue.

The Review fails to prove the validity of the assumption that the eight CFS and ME definitions represent the same disease or group of closely related diseases centered around "medically unexplained chronic fatigue." But more importantly, the Review ignores the substantial evidence in the literature that demonstrates this assumption to be false. In analyzing diagnostic methods, the Review focuses solely on the accuracy of the given diagnostic method itself as it applies to a given definition. The assessment of diagnostic methods ignores evidence of the lack of accuracy of the underlying definition and the resultant implications for the validity of the diagnostic method or its applicability across all CFS and ME case definitions.

It is scientifically unreasonable and unethical to make recommendations about diagnostics, treatments and harms in one patient population based on studies done in another patient population. Given the evidence that these definitions do not encompass the same

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populations, this Review must reassess the validity of its core assumption and the conclusions made on the basis of that assumption.

Flawed search methods. Inclusion/exclusion choices apparently shaped what evidence was considered and what conclusions were drawn, and to my mind reflect a poor understanding of ME/CFS research. Some examples of how the above assumptions and protocol choices negatively impacted this Review include:

- Evidence about the significant differences in patient populations and in the unreliability and inaccuracy of some of these definitions was ignored and/or dismissed. This includes: Dr. Leonard Jason's work undermining the Reeves Empirical definition; a study that shows the instability of the Fukuda definition over time in the same patients; studies demonstrating that Fukuda and Reeves encompass different populations; and differences in inclusion and exclusion criteria, especially regarding PEM and psychological disorders.
- Diagnostic methods were assessed without first establishing a valid reference standard. Since there is no gold reference standard, each definition was allowed to stand as its own reference standard without demonstrating it was a valid reference.
- Critical biomarker and cardiopulmonary exercise studies, some of which are in clinical use today, were ignored because they were judged to be intended to address etiology, regardless of the importance of the data. This included most of Dr. Snell's and Dr. Keller's work on two day CPET, Dr. Cook's functional imaging studies, Dr. Gordon Broderick's systems networking studies, Dr. Klimas's and Dr. Fletcher's work on NK cells and immune function, and all of the autonomic tests. None of it was considered. Also, the Review fails to discuss the diagnostic utility of CPET.
- Treatment outcomes associated with all symptoms except fatigue were disregarded, potentially resulting in a slanted view of treatment effectiveness and harm. This decision excluded Dr. Lerner's antiviral work, as well as entire classes of pain medications, antidepressants, anti-inflammatories, immune modulators, sleep treatments and more. If the treatment study looked at changes in objective measures like cardiac function or viral titers, it was excluded. If the treatment study looked at outcomes for a symptom other than fatigue, it was excluded.
- Treatment trials that were shorter than 12 weeks were excluded, even if the treatment duration was therapeutically appropriate. The big exclusion here was the rituximab trial; despite following patients for 12 months, it was excluded because administration of rituximab was not continuous for 12 weeks (even though rituximab is not approved for 12 weeks continuous administration in ANY disease). Many other medication trials were also excluded for not meeting the 12 week mark. Exclusion of these studies may also have biased the Review toward including more behavioral and exercise intervention studies, and fewer medication trials.
- Counseling and CBT treatment trials were inappropriately pooled without regard for the vast differences in therapeutic intent across these trials. This meant that CBT treatments aimed at "correcting false illness beliefs" were lumped together with pacing and supportive counseling studies, and treated as equivalent.

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- Conclusions about treatment effects and harms failed to consider what is known biologically about ME and its likely response to the therapies being recommended. This means that the PACE (an Oxford study) results for CBT and GET were not only accepted (despite the many flaws in those data), but were determined to be broadly applicable to people meeting any of the case definitions. Data on the abnormal physiological response to exercise in ME patients were excluded, and so the Review did not conclude that CBT and GET could be harmful to these patients (although it did allow it might be possible).
- The Review claims that its findings are applicable to all patients meeting any CFS or ME definition, regardless of the case definition used in a particular study. Seeing how disparate the patient populations and their physiological pathologies are between the definitions, this is obviously a false and unfounded assumption, and simply not the case in the real world and clinical settings.
- The failure to examine objective measures of function, combined with the failure to consider treatment studies that used biomarker changes such as viral titers, resulted in the exclusion of many studies. These studies would have changed the Review's conclusions about the effect of CBT and GET on function, and would have expanded the evidence on medication trials.
- The choice of inclusion and exclusion criteria made by the Review unreasonably excludes critical evidence on diagnostic methods and subgroups.

By choosing to not include the PubMed database in the search, it seems a number of relevant studies have been overlooked. Source:
<http://www.cortjohnson.org/blog/2014/10/15/ahrq-report-excluding-progress-exclusionary-factors-missing-studies/>

Severe well-known quality issues with individual studies were either not considered or ignored. The PACE trial in particular; the Review failed to examine any of the well-documented deficiencies in this study, which if considered would likely downgrade the Review's assessment of the trial.

Regarding treatments, the Review explicitly decided to focus on changes in only one(!) symptom, fatigue, and almost exclusively self-reported subjective measures over objective measures of functional capacity, thereby choosing to ignore the critical component PEM (correctly noted by the Review to be a hallmark characteristic of the disease), as well as all other well documented and studied symptoms such as pain or neurological, endocrine, cardiovascular, immunological, cognitive and muscular abnormalities; most of them objectively measurable/verifiable. Inexplicably reducing a neuroimmune illness such as ME to just one single diffuse symptom that can also be found in a myriad of other illnesses, and that can't even be measured objectively, is unacceptable.

Including studies that used changes in physiological measures like antibody titers would have broadened the number of interventions examined by the Review. Examining data on objective measures of physical function like activity would have not only broadened the evidence base, but would have introduced data that call into question the assessment of GET benefits. There is no question that the selection of outcomes measures ultimately changed the Evidence Review's conclusions, and the Review must explicitly acknowledge the

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detrimental impact of those a priori decisions.

The Review never questioned whether the disease theories underlying these treatments were applicable across all definitions. Yet again the failure to be clear and specific about what disease was being studied muddles the findings. It simply isn't reasonable comparing treatments like Rituximab/Rituxan or Ampligen (targeting a very specific objectively measurable biological issue) with talk and/or exercise therapies (thought to reverse what is assumed to be the patient's "false illness beliefs") by pretending that both types are about aimed at the one and same disease.

The issue of harms associated with CBT and Graded Exercise Therapy/GET has not been addressed adequately. Again a problem likely caused by the failure to be clear and specific about what disease was being studied. The Review ignored substantial evidence of harms associated with GET, thereby failing to recognize the evidence of well-known correlations between abnormal physiological responses to exercise (as evidenced by significant, distinct responses to exercise in gene expression and cardiopulmonary measures), Post Exertional Malaise/PEM, and harms following GET. This underplays the serious risk of harm for ME patients who are prescribed exercise, and creates a high risk that the Review will be used to perpetuate the harmful prescription of exercise to ME patients who are physically incapable of exercising without incurring harm. Patients who have an organic disease characterized by neurological, immunological and metabolic impairments would not have a meaningful therapeutic response to CBT (based on hypothetical "false illness beliefs") and would be at higher risk for harm. The Review must clearly acknowledge the harm done to ME patients when psychological theories and treatments are applied to a disease with demonstrated organic pathologies.

To claim that correcting patients' false illness beliefs could adequately treat multiple sclerosis or hypothyroidism would be malpractice and quackery. Similarly, a disease like ME characterized by multisystem dysfunctions and measurable physiological abnormalities cannot be credibly treated by convincing patients that they erroneously believe those physiological problems to exist. The reverse is also true: patients with the single symptom of chronic fatigue are not likely to respond to treatment with antivirals or immune modulators, in the absence of measurable immune dysfunction.

The Review misinterprets some of the papers expressing harms associated with a diagnosis. The Review fails to acknowledge the relief and value of finally getting a diagnosis, particularly from a competent and supportive physician. The harm is not from receiving the diagnostic label, but rather from the all too common delay in diagnosis and the subsequent response from incompetent healthcare providers.

At the same time, the Review failed to acknowledge the severe harm that patients face if they are given harmful treatments based on the mistaken belief that ME/CFS isn't a real biological illness, but a psychological or behavioral problem.

The bad science reflected in citing Oxford's flaws and then using Oxford studies anyway, as well as recognizing the importance of PEM but failing to consider the implications of Fukuda's and Oxford's failure to require it.

The Review excluded all studies examining biomarkers or physiological tests "because the intent of these was to identify an etiology rather than understand how the specific test could

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distinguish patients that would respond to treatment.” This choice means that hundreds if not thousands of studies were not considered at all, which had the indisputable effect of narrowing the evidence base monumentally. This limitation and its ramifications for the Review’s conclusions must be expressly acknowledged.

The Review noted a number of limitations on the evidence base including: that important studies may not have been identified; that other diagnostic testing studies may provide further insight into identifying patients with ME/CFS; that treatment studies shorter than twelve weeks were not included; that outcomes for symptoms other than fatigue were not included; that published studies may have been affected by conflicts of interest or bias; and that studies were generally of poor quality. We agree that all of these are serious limitations of this Review.

The Review failed to acknowledge that poor study quality is largely a result of the low levels of research funding available. It must be acknowledged as a factor affecting the evidence base. The ME evidence base cannot be properly assessed without understanding this critical limitation.

The Review correctly noted, “treatment of ME/CFS often involves multiple concurrent therapies” but also claimed that the Review’s “interventions and comparators represented most of the therapeutic modalities commonly used in clinical practice.” This is not true. Treatments used for ME patients include a number of medications and therapies excluded from the review including immune modulators, beta blockers, antihypertensives, antidepressants, antivirals, antibiotics, antifungals, stimulants, pain medications, sleep medications, IV saline, and manual physical therapy. The protocol used for the Review excluded almost all of this research. The Evidence Review must explicitly acknowledge this weakness in the applicability of its findings.

The Review stated that the lack of a gold standard for diagnostic comparison creates “an inherent risk of bias by the opinion of experts,” such as the identification of PEM as a critical feature without methods for testing and monitoring the symptom. However, this is a very one-sided view of bias. For example, a small number of researchers hold to the “fear avoidance theory” and/or “deconditioning and exercise intolerance theories of chronic fatigue syndrome” despite evidence to the contrary in patients with ME. On the other hand, there is a growing body of evidence around PEM and how to measure its effects, as well as objective proof of the phenomenon. Competing schools of thought are to be expected in areas of scientific controversy, but bias in the face of contradictory evidence is something different. The Evidence Review should acknowledge the risk of bias among all experts, and also explicitly acknowledge the objective evidence that contradicts such bias.

The Review failed to acknowledge that the most severely affected patients are unlikely to participate in studies like the ones included in this Review. To assume the widest possible definition means you draw conclusions about a population whose characteristics are unclear and even in part contradictory in diagnosis. Even with a more narrow definition, many studies lack data on severe cases of ME/CFS. With using the maximum population, that imbalance is getting even worse. This is an immense problem that has to be addressed adequately before the Review is issued in its final form. Most importantly, these patients are at an exponentially higher risk for great and irreversible harm when subjected to inappropriate treatments.

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I would like to point out the enormous disparity between the number of clinical trials assessing CBT and GET, and any other treatment approach. There is an immense need for more biomedical ME/CFS research, and I do hope to see this reflected in your coming recommendations. Also, larger, definitive studies on diagnostic biomarkers are required.

Also, I'm concerned by the lack of mention/discussion of possible subgroups based on differences in biological pathologies. This is a critical issue, especially when accepting eight disparate ME or CFS definitions as equivalent.

ME/CFS is a complex disease, and it demands expertise. It cannot be successfully evaluated by a panel of non-experts, based on a seriously flawed Review.

I fully support the comment Factual and Conceptual Errors in the Executive Summary of the Draft Comparative Effectiveness Review "Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)" Raise Questions of the Review's Fitness for Purpose, submitted [redacted for patient privacy] October 3, 2014.

Further, I fully support the comments submitted [Redacted for patient privacy], et al. on October 18, 2014.

Careful consideration of the above issues raises legitimate concerns about whether this Review will produce good science and sound recommendations.

I hope you will give my concerns a fair hearing, and that these issues are addressed before the evidence review is issued in its final form.

Sincerely,

Bianca Lindstrom
Anneli Magnusson
Lars-Eric Magnusson
Benita Meriaux
Anton Meriaux
Mireille Edgren
Hans Edgren
Åsa Kleberg
Sven-Erik Johansson
Vera Bengtsson

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We hereby submit the following text as a comment to the AHRQ Draft Systematic Evidence Review on Diagnosis and Treatment of ME/CFS.

We apologize for the fact that our English is somewhat poor (it is not our first language) and hope that the issues we raise will nonetheless be taken into consideration.

Sten Helmfrid Köpenhamnsg 24, 16442 Kista, Sweden
Britt-Marie Thurén
Anne Örtegren

Methodological problems in studies of cognitive behavioral therapy and graded exercise therapy as treatments for ME/CFS

Cognitive behavioral therapy and graded exercise therapy are sometimes recommended as treatments for ME/CFS. The underlying treatment model aims to change the patient's thoughts about the illness in order to enable them to recover by means of exercise. There are studies that claim positive results of these treatments, but they have serious methodological shortcomings. Objective data are lacking, and the selection of patients is not clearly defined. Negative physiological consequences of exercise have been shown in other studies, and independent evaluations by patient organizations confirm these negative consequences. Therefore, patients with ME/CFS should be advised against cognitive behavioral therapy and graded exercise therapy according to this model.

Introduction

ME/CFS – also known as chronic fatigue syndrome – is a severe illness that can be debilitating [1]. The World Health Organization (WHO) classifies it, since 1969, as a neurological illness [2]. The etiology and pathogenesis are unknown, but immunological and autonomous abnormalities, neuroendocrine dysfunction, anomalies in the brain and in the functions of mitochondria as well as cognitive impairments have been demonstrated in ME/CFS patients [3].

There is no effective treatment for the illness. During the 1990s a group of British liaison psychiatrists – the so-called Oxford school – presented the hypothesis that ME/CFS patients misinterpret signals from their body. Their “abnormal illness beliefs” are to be changed by means of cognitive behavioral therapy (CBT). This therapy is often combined with graded exercise therapy (GET), in which patients increase their activity levels according to a set schedule in order to recover through exercise. GET must not be confused with pacing, in which the patient learns to balance rest and activity and to be attentive to body signals. A number of studies have been published on cognitive behavioral therapy and graded exercise therapy for ME/CFS patients, for example the British PACE study from 2011 [4], which attracted media attention. The results are not unanimous, but several studies claim positive treatment results. However, these studies are seriously flawed and have been harshly criticized by researchers, clinicians and patient organizations [5–12]. This article

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reviews the methodological shortcomings and shows that CBT and GET according to the Oxford model do not give any positive effects for patients with ME/CFS; but may instead cause a deterioration of their condition.

Lack of objective data in the studies

The treatment results in the studies of cognitive behavioral therapy and graded exercise therapy have usually been evaluated by means of patient-reported surveys, where the patients themselves report their health status along a given scale [4]. It is well known that there is a placebo effect in subjective reports. The placebo effect has many causes, but among other things it is influenced by the attitude of the researcher. For this reason the systematic deviation can be expected to be large in the case of cognitive behavioral therapy according to the Oxford model, since the treatment aims at convincing the patients that the method works.

Double blind testing is not possible in the case of psychological intervention, but the activity levels of patients can be measured with a so-called actometer, a device the size of a wristwatch that is attached to the wrist or the ankle. It is important that activity be measured continuously over time, since ME/CFS patients tend to compensate for increased activity in one area with decrease of other activities. In most published studies of cognitive behavioral therapy and graded exercise therapy, objective measurements of activity level before and after treatment have not been included. This makes it difficult to assess how the functional level of the patients has been affected.

Objective measurements have only been presented on a few occasions. In one publication, a Dutch group reviewed three earlier studies of cognitive behavioral therapy and gathered data from actometers retroactively. The analysis showed that there had been no objective increase of patient activity level, even though the patients had reported a subjective decrease of fatigue in the surveys [13]. In another publication, neuropsychological test results before and after CBT treatment were compared. The self-reported cognitive functional impairment decreased with CBT, but objective test results remained unchanged [14].

Some studies have attempted to evaluate the treatment results of cognitive behavioral therapy and graded exercise therapy in a more objective manner, but the data gathered have been insufficient. In the British PACE study, the distance that patient managed to walk in six minutes was measured, and a minor increase was shown for the CBT and GET groups [4]. However, the walking test is a blunt measure of objective improvement, since it is not possible to control how much of an effort the patients make. Nor was the total activity level registered with actometers, so it is impossible to determine whether the general functional level of the patients improved. In a Dutch study of internet-based CBT for young people, school attendance was registered [15]. But study results were not measured, nor was there any check on whether increased attendance was compensated by a decrease in other activities. It is therefore not possible to reach any firm conclusions about changes in the functional level of the patients.

The final result of the walking test in PACE was an average of 354 meters for patients treated with CBT and 379 meters for the participants in the GET program. It should be noted that this is far from the reversal of the condition that the researchers claim is possible. For the sake of comparison, we can mention that a healthy person manages about 600 meters in a walking test. The limit where a lung transplantation is recommended for a person with

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lung disease is 400 meters [16], and in one American study of elderly persons with chronic heart failure, the most seriously ill group attained a result of 402 meters [17].

Ill defined patient groups

Another problem is that in many studies the diagnostic criteria and therefore also the selected patient groups have been unclear. Centers for Disease Control and Prevention (CDC) published the first criteria for chronic fatigue syndrome in 1988 after an outbreak in Lake Tahoe and introduced the concept of Chronic Fatigue Syndrome (CFS) [18]. The criteria were updated in 1994 [19], and this set of criteria – sometimes called “the Fukuda criteria,” after the first author – is the most commonly used in scientific publications about ME/CFS. According to these criteria, the disease is not considered just a form of long-lasting fatigue. Apart from chronic fatigue, patients must show four further symptoms from a list of eight symptoms that are neurological and immunological in character.

In 1991, the Oxford school published its own criteria for CFS, even though the name CFS was already in use and defined by the Fukuda criteria. The so-called Oxford criteria only require long-lasting severe fatigue [20], although the patients may also have other symptoms. Thereby a much larger and much more heterogeneous patient group is defined than that of the Fukuda criteria. Among other things, many patients with psychiatric diagnoses are included.

In 2003, an expert committee commissioned by Health Canada, prepared a consensus document about ME/CFS and published a new and stricter set of criteria, now usually called “the Canadian consensus criteria (CCC)” [21]. The purpose was to define a more homogeneous patient group. Among other things post exertional malaise (PEM) was emphasized as a mandatory symptom. Along with PEM, patients must show a large number of neurological, immunological and endocrine symptoms. This set of criteria is used by the International Association for CFS/ME (IACFS/ME) [3] and is recommended by most biomedical researchers in the field.

Evaluation and comparison of treatment studies of ME/CFS have been hindered not just by the many different sets of criteria but also by the fact that many authors have “operationalized” the diagnostic criteria. Usually operationalization means that the criteria are reformulated in order to make it possible to apply instructions in an experiment. In many studies of treatment with CBT/GET, the concept of operationalization has been twisted or some of the requirements of the criteria have been eliminated, all of which produces uncertainty as to whether the results really reflect the correct patient group according to a certain set of criteria.

Most early studies of CBT/GET were based on the Oxford criteria [22] or on operationalized Fukuda criteria [23]. More recently, studies using the complete Fukuda criteria have also been published [24]. It is not clear whether the results for a large heterogeneous patient group can also be assumed to be valid for a more strictly defined group, for instance patients that comply with the Canadian consensus criteria (CCC). One study from British primary care shows that the probability of a positive treatment result with CBT and GET in the case of long-lasting fatigue substantially decreased if the patients complied with criteria for ME/CFS (in this case the Fukuda criteria) [25].

In the PACE study, the Oxford criteria were used, but alongside this a comparison was made with the results for patients that simultaneously complied with the so-called London criteria

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[26] and the Reeves criteria [27]. Unfortunately, it is difficult to draw any secure conclusions from this comparison: only subjective results were included, and the strictest definition, the Canadian consensus criteria, was not used.

Physiological abnormalities indicate activity-induced deterioration

A number of studies indicate that activity causes a worsening of the condition of ME/CFS patients. A research team in the USA, led by Christopher Snell, studied the absorption of oxygen in ME/CFS patients during repeated exercise tests. The tests were carried out with an interval of 24 hours. In the first test, the ME/CFS patients demonstrated normal values, but, unlike controls, in the second test they showed a clearly reduced capacity of oxygen absorption, both at maximum level (VO₂ peak) and at the anaerobic threshold [28]. These results are completely compatible with the post-exertional malaise of which patients often complain, and which is a mandatory symptom in the Canada consensus criteria. Similar results have recently been published by another American group led by Betsy Keller [29].

Increasing evidence indicates that dysfunctions in the metabolic system related to the switch between anaerobic and aerobic energy production is causing the post-exertional malaise present in ME/CFS [30]. Patients should especially avoid "oxygen debt". The graded exercise therapy recommended by the Oxford school is aerobic. The results of the Snell group underline the importance of differentiating between different types of chronic fatigue. Fatigued patients with a primary depression improve with aerobic exercise, whereas in ME/CFS patients it induces deterioration, and if the ME/CFS patients also suffer from a secondary depression, their depression is simultaneously worsened [30].

An American study has demonstrated changes in gene expression of ME/CFS patients during 48 hours after exercise [31]. A British study has shown elevated concentrations of the inflammatory cytokine TNF- α three hours and three days after exercise [32].

Patient evaluations demonstrate problems with CBT and GET

Over time, patient organizations have repeatedly evaluated different forms of treatment through questionnaires. There are data available from ten independent surveys carried out in four different countries with more than 13700 patient responses [33,34]. The survey results confirm that graded exercise involves great risks for deterioration of health in ME/CFS patients. More than 4600 patients had tried this kind of treatment and altogether 52% reported that they felt worse.

The largest survey was done by The ME Association in the UK. In a comparison of various therapies, graded exercise therapy showed the lowest proportion of patients who had experienced improvement and the highest proportion that had experienced deterioration [35]. More than 56% of the patients got worse because of the treatment, and 33% reported that they had gotten much worse. Both in the case of graded exercise and that of cognitive behavioral therapy, a lower share of the patients reported improvement and a larger share reported deterioration than in the case of homeopathic treatments. Homeopathy is currently considered a pseudo-science, and the results of treatments according to this method therefore indicate the level of placebo effect. The same pattern was seen in a Norwegian patient survey [34].

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In the PACE study, the risk for deterioration in graded exercise therapy was studied. No relapses were reported and the authors concluded that the treatment is safe. This result stands in sharp contrast to all patient surveys. However, it is not possible to determine whether the patients increased their activity level according to the protocol of PACE, since actometers were not used. The walking test showed that the patients could walk 379 meters in six minutes, which is far from the goal of recovery through exercise. If the level of activity is increased, the risk for a relapse will increase. This can explain why graded exercise therapy so often leads to deteriorated health when put into continued practice. Therefore the conclusion that graded exercise therapy is a safe treatment is highly questionable.

The underlying theory lacks theoretical support

The Oxford school treatment model is based on two hypotheses, fear avoidance theory and deconditioning and exercise intolerance theory. The first one makes the assumption that patients are afraid of activity and avoid effort, and that this behavioral pattern perpetuates the symptoms. The second hypothesis suggests that symptoms are caused by deconditioning, due to the patients' low level of activity. The condition can be reversed by changing the thought and behavioral patterns of the patient [4].

These hypotheses seem dubious already at first sight. The presumed fear of activity disagrees with the push-crash cycles, which both patients and doctors report [36]. If deconditioning were to cause ME/CFS symptoms, as the second hypothesis claims, similar symptoms should be observed in persons who are inactive for other reasons, for instance persons who are put in plaster for a long period of time or prisoners in isolation. Nor has any reversal of ME/CFS through modified thought patterns been demonstrated, neither in PACE nor in any other study. The hypotheses are thus contradicted by the research results of its proponents.

The Oxford school has not been able to present any theoretical foundation for their ideas, although some attempts were made. Vercoulen et al published a structural equation model for ME/CFS, concluding that behavioral and cognitive factors contribute to the perpetuation of the illness [37]. However, the results do not justify such a conclusion. Structural equation models can be used to test causal hypotheses, but not to validate causal conclusions [38]. It is not possible to determine what is cause and what is effect among the biological, behavioral and cognitive factors present in ME/CFS without an understanding of underlying mechanisms; and this is not included in the model. Furthermore, Vercoulen used a heterogeneous group of patients. When the results were tested by other researchers, the model showed poor agreement for ME/CFS patients, but good agreement for patients with depression [39]. Harvey and Wessely have published a "model for understanding the etiology of CFS" [40]. The model consists of a figure showing how various factors interact in ME/CFS, but the authors do not describe any underlying mechanisms and do not explain how one should determine what is cause and what is effect in any given interaction. This "model" is therefore not an explanatory model in the scientific sense, but just a diagram of unfounded assumptions made by the authors.

Conclusions

A number of studies have been published on cognitive behavioral therapy and graded exercise therapy according to the Oxford model for patients with ME/CFS, and some of the

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studies claim that a modest but statistically significant improvement is obtained. However, when all the evidence is considered, there is good reason for questioning the usefulness of treatment with these methods and for being cautious about the risks for harm. No objective improvements have been demonstrated in any of the studies. The only objective evaluations that have been carried out of CBT indicate that the activity level and the neuropsychological functional level have not improved. Patient groups have been unclearly defined in many studies. It is highly uncertain if research on patients with general long-lasting fatigue is also representative for patients with neurological, immunological and endocrine symptoms along with fatigue.

Delayed physiological abnormalities have been shown in ME/CFS patients after exertion, for example changes in gene expression and decreased absorption of oxygen. This is confirmed by results from extensive independent patient surveys, demonstrating that a large proportion of patients have experienced deterioration in health – in the case of graded exercise therapy more than 50 %. The proportion of patients who have experienced improvement is on the level of the expected placebo effect.

There is no theoretical basis for cognitive behavioral therapy and graded exercise therapy according to the Oxford model. The underlying assumptions are contradicted by the Oxford school researchers' own results.

The usefulness of treating ME/CFS patients with cognitive behavioral therapy and graded exercise therapy according to the Oxford model cannot therefore be considered as based on evidence, and the risk for negative consequences means that health care professionals and patients should be advised against these forms of treatment. However, patients should be encouraged to engage in physical activity to the degree the disease allows, for example using pacing in order to find a balance between activity and rest. Cognitive behavior therapy with the aim to assist patients in coping with a serious disease can also be useful in many cases.

Usually, none of the methodological shortcomings discussed above appear in literature reviews or Cochrane publications. When health care authorities produce state of knowledge reviews, they normally use such compilations, and for this reason they often turn out to be misleading. It is vital to engage biomedical expertise and to critically review the original studies, as well as peruse the debate following their publication, for example in the form of letters to the editors in medical publications.

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Thankyou for the opportunity to comment on the Draft Report. Here are several suggestions:

*** Comment #1 (employment outcomes and the WSAS) ***

There appears to be significant oversights in relation to "employment outcomes" in the Draft Report.

Various measures are used, such as the Work and Social Adjustment Scale (WSAS). WSAS data from the PACE Trial was included under employment outcomes, but lost employment hours was not. This omitted data is in the following publication:

McCrone P, Sharpe M, Chalder T, Knapp M, Johnson AL, Goldsmith KA, White PD. Adaptive pacing, cognitive behaviour therapy, graded exercise, and specialist medical care for chronic fatigue syndrome: a cost-effectiveness analysis. PLoS One. 2012;7(8):e40808. doi: 10.1371/journal.pone.0040808. Epub 2012 Aug 1. PMID: 22870204. <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0040808>

The Draft Appendixes to the Draft Report indicates that this above mentioned paper was excluded because of "wrong outcomes". This was probably an oversight, because although the paper was primarily about cost-effectiveness and may have been excluded on that basis, employment and welfare outcomes were also included (and were not significantly different between the CBT, GET, SMC intervention groups). Employment outcomes and work hours are given importance in the Draft Report, so please reconsider the omission of this data. The PACE Trial was also the largest and best conducted study of its type and the important information about employment and welfare outcomes should not be excluded.

Furthermore, the WSAS is not an accurate measurement of "employment outcomes", it is more about "functional outcomes". Please examine the following reference and appendix for clarification: *"The Work and Social Adjustment Scale (WSAS) is a self-report scale of functional impairment attributable to an identified problem (Marks, 1986; see Appendix)."*

Mundt JC, Marks IM, Shear MK, Greist JH. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. Br J Psychiatry. 2002 May;180:461-4. PMID: 11983645. <http://bjp.rcpsych.org/content/180/5/461.long>

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Work and Social Adjustment Scale

Rate each of the following questions on a 0 to 8 scale: 0 indicates no impairment at all and 8 indicates very severe impairment.

- Because of my [disorder], my ability to work is impaired. 0 means not at all impaired and 8 means very severely impaired to the point I can't work.
- Because of my [disorder], my home management (cleaning, tidying, shopping, cooking, looking after home or children, paying bills) is impaired. 0 means not at all impaired and 8 means very severely impaired.
- Because of my [disorder], my social leisure activities (with other people, such as parties, bars, clubs, outings, visits, dating, home entertainment) are impaired. 0 means not at all impaired and 8 means very severely impaired.

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- Because of my [disorder], my private leisure activities (done alone, such as reading, gardening, collecting, sewing, walking alone) are impaired. 0 means not at all impaired and 8 means very severely impaired.
- Because of my [disorder], my ability to form and maintain close relationships with others, including those I live with, is impaired. 0 means not at all impaired and 8 means very severely impaired.
-

*** Comment #2 (objectively measured physical activity) ***

Activity levels as measured objectively by actigraphy have demonstrated that CBT which incorporates GET does not increase the illness-induced decreases in physical activity. This provides important context to the 'rehabilitation' model of CFS and the expectations of patients who do CBT/GET. The following publication is a meta-analysis of 3 trials of CBT which included GET:

Wiborg JF, Knoop H, Stulemeijer M, Prins JB, Bleijenberg G. How does cognitive behaviour therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity. *Psychol Med*. 2010 Aug;40(8):1281-7. PMID: 20047707.

<http://www.ncbi.nlm.nih.gov/pubmed/20047707>

*** Comment #3 (withdrawal rates in the PACE Trial) ***

The Draft Report states that: *"The PACE Trial described previously was a large 12-month good-quality trial (n=641) comparing four interventions: CBT; GET; an adaptive pacing therapy; and a usual care control group.[98] Attrition was low with only 1.7 percent withdrawing overall and adherence was not reported."*

However, when reading the 2011 Lancet paper (see below URL) there appears to be 53/641 (8.3%) formal withdrawals and an additional 32/641 (5.0%) lost to followup. It is unclear how the figure of 1.7% was calculated.

<http://www.thelancet.com/journals/lancet/article/PIIS0140673611600962/images?imageId=gr1§ionType=red>

*** Comment #4 (caveat on case definitions) ***

The Draft Report states that: *"We elected to include trials using any predefined case definition but recognize that some of the earlier criteria, in particular the Oxford (Sharpe, 1991) criteria, could include patients with 6 months of unexplained fatigue and no other features of ME/CFS. This has the potential of inappropriately including patients that would not otherwise be diagnosed with ME/CFS and may provide misleading results."*

This rather important caveat should be given greater prominence in the overall report and any summary if it is a fundamental problem which could undermine the conclusions of the entire review.

*** Comment #5 (when are non-blinded trials 'good quality') ***

According to the Draft Report:

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"Good-quality studies are considered likely to be valid. Good-quality studies clearly describe the population, setting, interventions, and comparison groups; use a valid method for allocation of patients to interventions; clearly report dropouts and have low dropout rates; use appropriate methods for preventing bias; assess outcomes blinded to intervention status; and appropriately measure outcomes and fully report results."

"Fair-quality studies have some methodological deficiencies, but no flaw or combination of flaws judged likely to cause major bias. The study may be missing information, making it difficult to assess its methods or assess limitations and potential problems. The fair-quality category is broad, and studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are likely to be valid, while others are probably invalid."

Not many studies are described in the Draft Report as "good-quality". The PACE Trial was described as "good quality" but other CBT/GET trials as "fair-quality". Although the PACE Trial is larger and better conducted than other CBT/GET studies, it may not be accurately described as "good-quality" according to the criteria listed above for good quality studies: *"use appropriate methods for preventing bias; assess outcomes blinded to intervention status; and appropriately measure outcomes and fully report results"*.

The PACE Trial was an open-label study which did not blind its participants, providers, or assessors. The difficulties of blinding in such a trial does not negate the fact that non-blinded trials are problematic. This opens up the trial results to a range of biases, particularly when two of the tested therapies are aimed at changing participants' beliefs and perceptions about their self-reported symptoms and impairments, and when the more objective outcomes do not support the self-reported improvements. This is not to say that the PACE Trial has no value and should not be included, but questions the elevation of its status to "good quality" when the same would not be done to non-blinded pharmacological trials.

Many of the pre-defined outcomes in the PACE Trial protocol (URL below) have been greatly altered or have not been published:

<http://www.biomedcentral.com/1471-2377/7/6>

***** Comment #6 (what are the negative effects of a CFS diagnosis?) *****

The Draft Report states that "the negative effects of being given a diagnosis of ME/CFS appear to be more universal".

It is not clear what these supposed negative effects are, and should be made more clear in the summary.

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To: Scientific Resource Center

Portland VA Research Foundation

Subject: Comments on the AHRQ Evidence Review

Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Date: October 20, 2014

I have had two goals in taking many hours to write these comments. I wish first to forward and pursue the interests of citizens of the United States, in respect of the AHRQ Evidence Review as contracted for and specified by employees of the National Institutes of Health, an agency of the executive branch of the U.S. government.

To this end, I wish secondly to make known for the benefit of the Review's authors and revisers the historic events dating from 1984 to the present which resulted in construction of the name "Chronic Fatigue Syndrome" and its application to the Incline Village, Nevada outbreak of the disease formerly known as Myalgic Encephalomyelitis and designated at 93.3 under neurological diseases by the WHO. This history also encompasses the confounding and spoilage which occurred to this AHRQ Evidence Report by misapplication of the name "Chronic Fatigue Syndrome" in the United Kingdom to altogether different non-biomedical psychological phenomenon which have already fated British patients to mistreatment and now threaten Americans should their incorporation into the AHRQ evidence review prevail.

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The AHRQ Evidence Review suffers from massive misunderstanding of the term “Chronic Fatigue Syndrome” (CFS) and the condition it describes. The reviewers accept application of the CFS term indiscriminately, confusing a wide range of disease definitions to great harm. They not only mix apples and oranges, but also papayas, mangos, gooseberries and parsnips. Accuracy and specificity are needed. The following distinctions must be understood and included.

This term “Chronic Fatigue Syndrome” (CFS) originated with the CDC in 1988. It was coined to describe specifically the disease and symptoms as presented in the devastating and incomprehensible outbreak that afflicted more than 300 persons in and around the semi-rural Lake Tahoe resort of Incline Village, Nevada, beginning in the winter of 1984-85.

In 1988 U.S. officials assembled medical experts to assign a name to the Incline Village disease. Clinicians who have previously treated the disease then known as Myalgic Encephalomyelitis (M.E.) immediately recognized the symptoms and presentations as such.

The name Myalgic Encephalomyelitis originated in a 1950s article in the British Medical Journal (BMJ), which concerned itself with a recent outbreak at London’s Royal Free Hospital.

This name was made official in 1968 by the World Health Organization (WHO) which concurrently defined the disease as neurological. Subsequently it would be further established that the Tahoe-area outbreak and thousands upon thousands more cases in the United States and abroad also comprised Myalgic Encephalomyelitis (M.E.)

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Nonetheless, the CDC re-christened the Nevada outbreak of Myalgic Encephalomyelitis with the wholly misleading name “Chronic Fatigue Syndrome.”

The expression “chronic fatigue” conjures up for most people the universal over-tiredness of the modern era – something a long sleep and a week in the country would be bound to cure. Thus the re-christening has had the effect of causing severely incapacitated patients to be characterized as hypochondriacs and malingerers, and, most importantly, to be deprived of medical research and care.

Further, the term “chronic fatigue” is unhelpfully unspecific. Fatigue is a universal byproduct in mankind’s biological struggles. Chronic fatigue is widely recognized in cancer, multiple sclerosis, infections, pregnancy and more.

Worse yet, because of this erroneous name one million American citizens have been deprived of federal government protections to which they are entitled; notably, seriously undertaken research and implementations to be carried out by the NIH and the CDC.

In truth Myalgic Encephalitis – which is what patients suffer, despite the re-naming – features immune systems gone haywire, neurological systems and brains perennially plagued by a person’s own immune systems, dysregulating and de-regulating of hormones and body energy production systems. Pathogens and toxins appear to set off this miserable cascade. All of the dsDNA viruses are implicated, especially HHV-6 and Epstein Barr, along with parvovirus-19, mycotoxins and more.

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Whatever the cause, the patient loses cognitive function, memory, and concentration. Pain can be terrible and endless. Orthostatic dysfunction unsteadies one's efforts to sit and stand. Above all, M.E.'s singular and defining symptom is that exertion, more often physical but also mental, will be followed by body and brain failing to recover function within normal parameters. Shortfall in cellular energy production may be involved, but research has not been funded. In any event this key identifying phenomenon is known as "post-exertional malaise" (PEM.) (Please note that "collapse," not "malaise," is the real issue.)

Thus fit and capable citizens become transformed by the disease into the equivalent of broken down jalopies -- *sans* spark plugs, *sans* gasoline, *sans* hope. Gone is their ability to function as productive members of society and participants in family and community life. In hard dollars the cost to the United States alone is estimated at \$40 billion annually in lost productivity.

Key to the CDC's mis-naming was ignorance. Following the 1984-85 outbreak, local doctors eventually prevailed on the CDC to send two staffers up the Sierra Nevada to take a look in late 1986. But the CDC's effort was *de minimis*. No decent university department of epidemiology would recognize it as such. The Epidemic Intelligence Service officer assigned the job walked out after a week. His rookie assistant stuck it another week, but could manage only scanty study of patients. Nor was further research ever conducted at Incline Village or sites of other extensive outbreaks, such as Lyndonville N.Y.

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At the same time, the Incline Village outbreak attracted a cloud of fierce political pressure. Everyone from local Chamber of Congress to political representatives wanted the thing to just go away; as second choice they discouraged talk of serious disease in order to preserve Tahoe's reputation as a safe tourist destination. In addition, some observers allege that insurance companies resisted official naming of yet another serious bio-medical disease to follow the expenses of HIV-AIDS.

All in, almost everyone presenting with the Incline Village malady, like so many other diseases, complained of being excessively tired. That made it ever so easy for CDC to wrongly assign the label "Chronic Fatigue Syndrome" (CFS) to hundreds, and then thousands, and ultimately hundreds of thousands, of cases of Myalgic Encephalomyelitis. But this re-christening alone need not have led to tragedy – tragedy for one million or more Americans and roughly 17 million persons more worldwide. After all, much re-naming goes on without causing much harm, other than re-printing stationary and re-identifying financial accounts.

For example, consider a person named Judy Jones. On marrying Bob Smith, Judy might well henceforth take the name Judy Smith. Nonetheless, our Judy will be the very same person-- same appearance, same bank account, same faults, and same Mom and Dad.

But imagine the outcome if Judy, shortly after marrying Bob, were to then fall prey to identity theft. Other persons and entities could begin presenting themselves here, there and everywhere as Judy Smith. Someone or something bearing the name Judy Smith might suddenly charge thousands in computer games on a Visa card. Judy Smith seems to be a

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computer freak, after all, not a newlywed! But then in the Cayman Islands someone named Judy Smith opens a bank account into which pour millions of dollars each month. Judy Smith is no newlywed, but rather the hard-bitten leader of a Columbian drugs cartel!!!

Subsequently there may emerge Judy Smith the porn star, Judy Smith the teen-age runaway, Judy Smith the astrologer, and...

So it was with “Chronic Fatigue Syndrome.” A very long and complicated story attaches to the evolution of the British versions of “CFS,” constructed by a small but powerful group of psychiatrists. However identity theft – the theft of the American name and its assignment to new psychological conditions of their own creation -- was the first and crucial step towards the “CFS” empire of fame and fortune which they would eventually build.

The British versions began with elaborate theorizing rather than the empirical data, however paltry, that the American naming had relied on. Their theory asserts that “false beliefs” and “deconditioning” lay behind the complaints of un-wellness accompanied by fatigue which Britain’s general practitioners (GPs) were likely to hear. The theorizing sprung fully formed from a psychiatrist’s imagination, rather like Athena from Zeus’ head. While quite legally appropriating the un-trademarked name of Chronic Fatigue Syndrome, they named two new definitions for their creation “Oxford Definition” and “London Definition.”

The AHRQ Evidence Review must reflect that neither is to be considered in any way synonymous with the “Chronic Fatigue Syndrome” derived from the Incline Village

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outbreak of Myalgic Encephalomyelitis, and laid out, albeit imperfectly, in the Fukuda definition.

The U.K. - invented definitions of “CFS” do not involve immune dysfunction, neurological symptoms. infections, sore throats, swollen glands, new headaches, or myalgias, all of which are cited in the U.S. disease. Most important, they do not recognize Post-exertional Malaise (PEM.) Mainly it seems they are characterizing clinical depression not previously diagnosed.

“But how is this possible,” a person might well ask. Happily for the U.K. psychiatrists, artifacts of National Health System (NHS) regulation and custom, such as tight limits on expensive testing, allow the erroneous definitions to persist. Once a patient is labeled with the “CFS” definition they may not be investigated for other ailments. They will not receive any treatment other “activity management” relying on CBT and GET. When an adult patient refuses such “treatment” he or she sometimes finds themselves “sectioned,” meaning committed to a mental hospital. A parent who differs on “CFS” care with the NHS will often have to mount a legal battle or see the child taken into care.

One result for the U.K. has been a recent paper that reported at least one third of persons identified as having CFS by the NHS in fact are suffering from other diseases, such as Behcet’s syndrome, that might have been relieved with proper treatment. This may save money for the NHS (or not – see below) but it stands to cost the Exchequer enormously from livelihoods lost.

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Yet the psychiatrists have managed to establish and fortify their versions of “CFS,” even internationally, by running many trials of their proposed treatments – Cognitive Behavioral Therapy (CBT) and Graded Exercise Therapy (GET.) The manipulation of data is an old art, and these psychiatrists sliced and diced their trials so that they resulted in a great many papers, approved by close colleagues at U.K.-based medical journals. The numbers helped them climb in important computer-based grading of research according to numbers of citations, and allowing them to become quite eminent despite scant real research. Political connections and a concurrence of interests with the benefits-cutting government of Prime Minister Tony Blair helped them to extensive funding and national eminence. The \$8.7 million Pace Trial was the consummation.

The PACE Trial, alas, did not go as planned. The Protocol specified outcomes of improvement for patients receiving CBT and GET that involved significant increase in levels of activity. As the trial proceeded it became obvious to the trial supervisor that the desired improvements were not happening.

Rather than lose the game the supervisor moved the goal posts. Activity meters had been meant to be worn by trial participants afterwards to measure objectively the increases in activity the trial’s authors expected. Suddenly it was decided that wearing the watch-like instruments would be too exhausting for these individuals, however supposedly strengthened by CBT and GET. And the number chosen as the cut-off for measuring improved status with a questionnaire was lowered by more than 25% -- from 85 to 65. Actually, 65 had been the mark for patients considered unwell enough to enter the trial to

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begin with. So a person could start off unwell and end up unwell and yet be pronounced recovered, thanks to the wonders of statistics.

And so Britain's Medical Research Council held a press conference to announce the trial's completion. The world's press was invited and attended with interest. The MRC press release declared the trial a great success proving the worth of CBT and GET for "CFS". The world press duly reported the contents of the press release. Having no way of knowing that "London" and "Oxford" brands were the syndromes under study, and that Fukuda-defined "CFS" had little in common, they reported an upbeat outcome to world attention. Indeed, confusingly, these continue to be the prescription even of the U.S. CDC on its web page – though of course it does not reflect any trial of the disease one might call by the name "CFS" in the US. (The relationship and influence of UK psychiatrists during the 20 year-long tenure of William Reeves as CDC's "CFS" chief is relevant, but too complicated and not necessary to these comments.)

It is likely that the PACE trial will be proved fraudulent and retracted in the long run. Thus for the AHRQ Evidence Review to heavily weight and indeed propagate its fraudulent message in defining the future research goals of the United States of America would seem to be irresponsible if not illegal in respect of the interests of US citizens and taxpayers.

Meanwhile British investigators are being held off from the raw data by refusals of participating institutions to meet FOIA requests. The British establishment as usual has reflexively closed ranks in the first instance, and a court decision failed to support the FOIA

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request. But it is early innings, and Britain's traditional favorite spectator sport, cricket test matches, can go on for days.

Psychiatrists belonging to the "CFS" clique meanwhile are thriving on the dividends from "Oxford CFS" and "London CFS." A private company part-owned by one or more is earning a great deal of money from contracting to supply CBT and GET services to private insurers and the National Health Service alike. The company is registered in Hamburg, Germany, so little may be learned about its business. But NHS staff have calculated that the cost is turning out to be a great deal more than anticipated. The Blair government's embrace of the doctrines of CBT and GET is not working out well for the U.K. financially. Nor has it worked out for the patients – they have not returned to work and school.

This AHRQ Evidence Review is meant to provide an agency of the United States government guidance in researching for the interests and welfare of the citizens of the United States.

The very heavy weighting of dubious and specious work by British psychiatrists, using definitions entirely at odds with U.S. medical descriptions of the disease, has hopelessly compromised the review.

I conclude in noting that the extensive threats to the interests of American citizens by errors, omissions and erroneous weighting of data contained within the AHRQ Evidence Review stand are well-explicated in the Comments submitted by Mary Dimmock, Jennie Spotila, et alia. I endorse their explanations and insights

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October 19, 2014

Comments on the AHRQ Draft Comparative Effectiveness Review on the Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

"HOLD! HOLD! HOLD!" This is what everyone in the chain of those responsible for mission assurance say in my profession of launching satellites into space when there is a problem detected with the launch vehicle, the satellite, the software, the ground systems, anything that could possibly impact the orbital injection of the payload. Calling HOLD HOLD HOLD can happen even in the last seconds of a count-down, and is the right thing to do even though it will disappoint people high up in the chain of command and delay agendas and timelines. Human safety and mission assurance far exceed all that. We don't hold a launch until the anomaly is resolved, regardless of the political fallout. We are given this authority because it is the right thing to do.

It may be easy to understand that lives are at stake when a rocket—even an unmanned one—is launched; should it go off course, human lives are at risk. Your task is not dissimilar. As the husband of a person with ME*, I am calling HOLD HOLD HOLD after studying the AHRQ Draft Systematic Evidence Review on Diagnosis and Treatment of ME/CFS. It is unsafe to proceed with the plans as they have been designed, for the current path will lead to *less* efficacy and *greater* harm for the proposed medical and nonmedical interventions to treat ME in adults.

I am professionally trained to review engineering data, uncover anomalies and develop resolutions. I ensure the anomaly is driven to root cause, and evaluate go-forward plans for efficacy and thoroughness. A collaborative environment of all stakeholders and experts is the only way this works. Our engineering review boards include people with knowledge, experience and insight into how the system works and what needs correction to ensure the system functions as designed.

The AHRQ has left out the stakeholders and the experts: the patients with ME and the experts in the field. Regardless of the AHRQ staff's training and professionalism, the brain trust that has developed treating patients and studying the root causes of ME for three decades cannot be ignored. They are the only people with the expertise to lead this process. The AHRQ can't achieve its goals without engaging them.

*Endorsing and echoing the comments submitted by [Redacted for patient privacy]., I use the term ME.

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In addition to excluding the best minds for the task, the AHRQ has ignored the critical disciplines: etiology; immune, cardiopulmonary, neural, and autonomic biomarkers; as well as Post Exertional Malaise that is crucial to defining the illness of ME and differentiating between those who have it and those who are fatigued, even chronically, because of any number of other conditions. Without this distinction the AHRQ does not have a precise population for which to compare studies.

Let me illustrate my points with a personal perspective. My wife Carollynn Bartosh has been disabled by ME for more than ten years. She was an ambitious professional and a model of good self care; she was the last person I would have thought was headed for a chronic illness.

When Carollynn got sick, we were fortunate that our GP sent her to Dr. John Chia, an infectious disease specialist and ME clinician/researcher nearby, who measured in her blood elevated, reactivated levels of EBV, HHV-6, Chlamydia pneumonia, an enterovirus, and the enterovirus Coxsackie B5. At the time, she was diagnosed with CFS. There have been few treatments to try, mostly off-label uses of drugs developed for other conditions, but we've tried everything. We realized early on that most other doctors think CFS is a form of depression, that they thought "fatigue" was her big complaint despite witnessing her symptoms and diagnosing several other bio-organic conditions commonly concomitant with ME: Postural Orthostatic Tachycardia Syndrome (POTS), Neurally Mediated Hypotension (NMh), interstitial cystitis (IC), an IGG deficiency, and a slew of serious allergies and sensitivities to foods and medicines. The state of medical practice meant that we had to learn as much as we could about the science of her condition to best help her.

Meanwhile, we knew that activities my wife loved and might feel well enough to enjoy on one day, like a family birthday gathering or a nice hike in the local hills, could lead to an exacerbation of all of her flu-like symptoms, symptoms that correspond to one or another of that cocktail of pathogens Chia found, and may render her home-bound for a week or two.

In time shingles, Varicella Zoster Virus/VZV, came into the mix for her, a very atypical presentation for the general public but typical of someone with a severely compromised immune system, such as with HIV, and for five years she's had break-through flare ups over most of her body despite remaining on the highest acute dose of antivirals. She has VZV-related hearing loss in one ear and sees her ophthalmologist every few months to keep tabs on the shingles she's had in her eyes.

The exceptional memory she used to have is spotty at best. The company she worked for before she got sick would say she was the glue that held their operations together, and it was her memory that made us marvel, her ability to hold multiple and complex threads of activities, internal and external relationship networks, working budgets, agendas, and plans. The person who could tell me what I was wearing on a particular outing four years ago can't remember if she's given our cat his daily medicine without leaving a trail of visual cues. When we make dinner together we sometimes can't talk if we're following a recipe because she can no longer hold an instruction in mind while hearing about my day.

Before Carollynn became sick she used to drag me on vigorous morning walks four days a week, training for our vacations hiking at altitude. She loved to garden and prided herself in doing all the heavy work, alongside the big guys we'd hire to help, too, insisting that it was good exercise and escape time from her busy professional life. Feeling sick with flu-like symptoms after exercise was one of the first clues to us that something was wrong, and soon, as she became more ill, feeling like that after mental activity as well. Now, after nominal physical or mental activity even on a "good day" she may experience a flare-up of shingles a few days later. Dr. Chia believes that VZV will be resolved when the underlying immune dysfunction of ME is understood and treatments are found.

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Until then, there are many aspects of her condition that we have little control over. Her mental health, however, is not one of those. Amazingly, she is not also depressed.

In 2007, three years into disability, we were thrilled that the leading clinicians and researchers changed the name of the illness from CFS to ME, and soon accepted the Canadian Case Definition with PEM as its central feature. Five years in, we found the Lights' first exercise studies in Post Exertional Malaise the most validating, targeted science to date. We made a flyer from the CFIDS Assoc. webinar materials to share with our doctors, family, and friends—and I have seen every doctor sit up to take notice (see below). We followed the subsequent studies by Stevens, Snell, Davenport, and VanNess into VO2max and anaerobic threshold, applying their subsequent safe exercise protocols with following my wife's heart rate not just during careful laying and sitting exercises but throughout activities of daily living. As an engineer I see that being able to quantify differences between healthy adults and those with ME is a great move forward. As I plotted her daily heart rate, we were not surprised to find the tachycardia typical of ME but also some troubling readings, too, that appeared to be bradychardia.

We read more studies about cardiac anomalies in ME such as Bell's low blood volume study and Peckerman's on heart failure, Jason's on causes of death in ME—studies from ten, fifteen years ago that should have received more attention, that should by now be part of standard knowledge for treating ME patients.

When the cardiologist who performed the tilt table test in which Carolynn fainted told us that he “doesn't believe in ME/CFS,” we went to a different doctor. He performed a 48-hour Holter monitor test. Through it we learned that what appeared to be bradychardia is arrhythmias, yet he would not engage any of the literature about blood volume that could be related and said that anti-depressants are sometimes prescribed for this condition.

After we brought these studies of low blood volume to the attention of our supportive GP, he was able to authorize four weekly infusions of IV-saline for her—not because of her ME diagnosis but because of POTS—resulting in my wife's POTS and NMH numbers improving dramatically and the arrhythmias abating. Her heat intolerance, which should have been problematic during the worst heat wave of the year, also abated. Because of delays in insurance authorizing further infusions, it has been two weeks since her last one. We can see in her daily heart rate charts that she has lost all the ground she gained. We hope the authorization for continuing the infusions will be forthcoming, but we are concerned they may not be approved because of the lag between scientific discovery and clinical practice.

All of the studies that validated our experiences, corroborated her symptoms, gave us criteria for measurement and the ability to document change, that brought some relief and a basis for looking for improvement over time in this story have been left out of the AHRQ review. Those studies as well as Chia's delving into “smoldering viruses” and every other study by researchers related to pathogens and post-viral syndromes, possible root causes, and other studies that the current AHRQ have found too small for inclusion are precisely the ones that physicians in general practice need to know about—now, even before the whole nut of ME has been cracked—in order to stop harming and begin helping patients. It is faulty review criteria that excludes this most promising science. It needn't be the case.

As if it is not enough for patients to languish for years and decades without real treatment options, when doctors have been told by the NIH that ME is the same thing as CFS, only treated with CBT and GET, they do not take seriously the constellation of symptoms that reveal that ME can be fatal. Our

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friend Hugh, who had been enjoying great improvement in his ME after being disabled for 25 years, went to an emergency room with severe upper abdominal pain. He was sent home with a diagnosis of stomach flu. Two weeks later he went back to the ER and was finally diagnosed in heart failure. By that time, his heart was seriously damaged. The doctors had not driven Hugh's health anomaly to root cause because they lacked the knowledge and direction that should be in place now for patients with ME. Hugh is alive, with a pace maker now, but living at a substantially reduced level of ability and well-being. But how many Hughs are out there? How many have not survived because the protocols are poorly constructed? These are just some of the harms that the system has in place now. And the trajectory of the path the AHRQ has set in motion now will only end up in this same place.

This totals up to a NO-GO for launch into achieving the goals of the AHRQ.

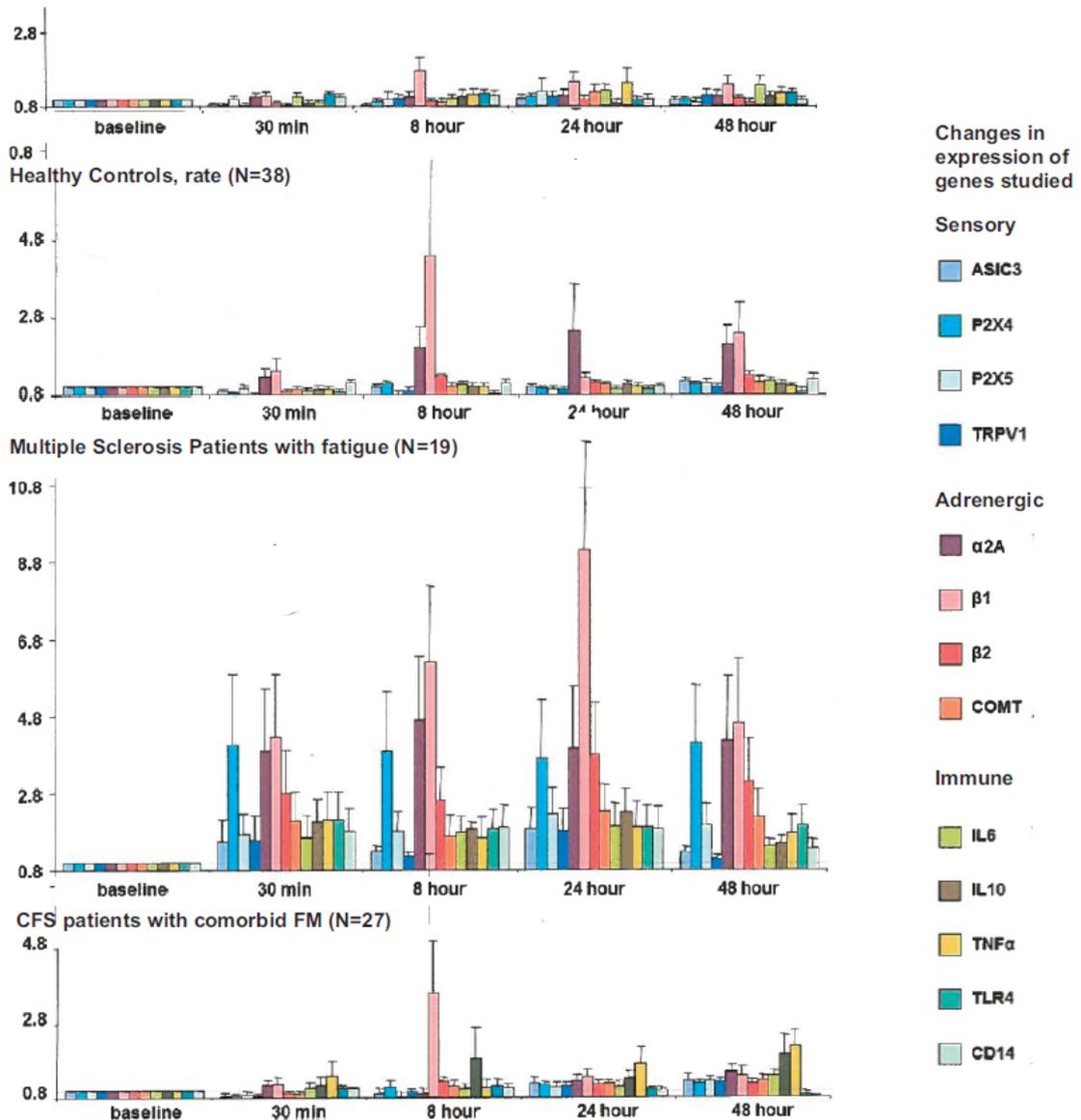
Luckily, the AHRQ effort is still early in its process; it can correct the problems and launch at a later date to arrive at the helpful outcome that is intended. To do so, the AHRQ must redefine its objectives. As I have noted earlier, the first and most significant step is developing an accurate statement of initial starting assumptions: what defines ME. Then engage the ME experts, the brain trust, to participate in forming the *starting* assumptions. Then you can examine the health anomaly that is ME with a lens that allows the unbiased development of root causes, that take into consideration all the relevant and critical disciplines, so that an accurate initial set of assumptions can be assembled and applied to the proper population. My wife is part of that population; please keep her alive.

The flyer [redacted for patient privacy] made with the graphs from the Light study for personal use only to share with her doctors, family, and friends.

Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects.

Light AR, White AT, Huguen RW, Light KC. *Journal of Pain*. 2009 Oct;10(10):1099-112.
doi: 10.1016/j.jpain.2009.06.003. Epub 2009 Jul 31. PMID: 19647494

Changes in gene expression after 25 min. of exercise to 70% of predicted maximal heart rate for Healthy Controls, MS, and CFS with fibromyalgia (FM)



Healthy athlete high intensity exercise Controls at times indicates after 25 min. of full body exercise to 85% of predicted maximal heart rate

Expanding Research: Building on Your Investment 2010 Webinar Series, Sponsored by the CFIDS Association of America, October 5, 2010. "Novel Ion Channel-based Biomarkers in CFS," slides 10 & 11, Kathleen Light, Alan Light, Lucinda Bateman, Andrea White, and Ron Huguen, Department of Anesthesiology, University of Utah. Jan.14, 2012. <<http://www.cfids.org/webinar/slides-100510.pdf>>

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Key Concerns about the PACE trial

Professor Malcolm Hooper September 2013

Introduction

Not only has Myalgic Encephalomyelitis (ME, also known as chronic fatigue syndrome or CFS) been classified as a neurological disorder by the WHO since 1969, but on 16th August 1992, the Rt Hon Stephen Dorrell MP, UK Minister of Health, went on public record confirming that: *“ME is established as a medical condition”*. The Department of Health officially accepts it as a chronic neurological disorder and since 2003 ME/CFS has been classified in the UK Read Codes used by all GPs as a neurological disease (at F 286). Furthermore, since its inception in March 2005 the UK National Service Framework on chronic neurological conditions includes ME/CFS, and the Department for Work and Pensions has confirmed in writing that it does not consider ME/CFS to be a mental disorder (letter of 21st November 2011 to the Countess of Mar signed by Lord Freud, Minister for Welfare Reform).

It thus cannot be referred to and treated as a behavioural disorder, but that is exactly what happened in the PACE trial.

Professor (now Sir) Simon Wessely directed the management of the PACE trial; he is a psychiatrist who is internationally known for his insistence that ME does not exist other than as an aberrant belief: *“I will argue that ME is simply a belief, the belief that one has an illness called ME”* (9th Eliot Slater Lecture, IoP, 12th May 1994). He disagrees with the WHO's classification and in defiance of the significant international evidence-base of organic pathology, he and his close colleagues have strived for over two decades to reverse the WHO classification of ME from neurological to psychiatric.

It was as long ago as 2000 that Anthony Komaroff, Professor of Medicine at Harvard and a world leader in ME/CFS, summarised in The American Journal of Medicine the key areas in which ME/CFS differs from psychiatric illness:

“Objective biological abnormalities have been found significantly more often in patients with (ME/CFS) than in the comparison groups. The evidence indicates pathology of the central nervous system and immune system. Autonomic nervous system testing has revealed abnormalities of the sympathetic and parasympathetic systems that are not explained by depression or physical deconditioning. Studies of hypothalamic and pituitary function have revealed neuroendocrine abnormalities not seen in healthy control subjects. There is considerable evidence of a state of chronic immune activation. In summary, there is now considerable evidence of an underlying biological process which is inconsistent with the hypothesis that (ME/CFS) involves symptoms that are only imagined or amplified because of underlying psychiatric distress. It is time to put that hypothesis to rest” (The Biology of the Chronic Fatigue Syndrome. Am J Med 2000:108:99-105).

Even earlier, in 1994, one of the world's most renowned ME/CFS clinicians, Dr Daniel L Peterson from the US, went on record: *“In my experience, it is one of the most disabling diseases that I care for, far exceeding HIV disease except for the terminal stages”* (Introduction to Research and Clinical Conference, Fort Lauderdale, Florida, October 1994; published in JCFS 1995:1:3-4:123-125).

In 1995, Professor Mark Loveless, Head of the AIDS and ME/CFS Clinic at Oregon Health Sciences University said in his Congressional Briefing that an ME/CFS patient: *“feels effectively the same every day as an AIDS patient feels two weeks before death; the only difference is that the symptoms can go on for never-ending decades”*.

In 2004, Dr William Reeves, Chief of the ME/CFS research programme at the US Centres for Disease Control, (CDC) reported that ME/CFS patients *“are more sick and have greater disability than patients with chronic obstructive lung or cardiac disease, and that psychological factors played no role”* (Press Release, AACFS, 7th October 2004).

Also in 2004, a randomised clinical trial found *“In comparison with other chronic illnesses such as multiple sclerosis, end-stage renal disease and heart disease, patients with (ME)CFS show markedly higher levels of disability”* (Am J Occup Ther 2004:58:35-43).

On 15th October 2009, Professor Nancy Klimas, then Professor of Medicine, Microbiology and Immunology at the University of Miami, famously said in the New York Times: *“I hope you are not saying that (ME)CFS patients are not as ill as HIV patients. I split my clinical time between the two illnesses, and I can tell you that if I had to choose between the two illnesses I would rather have HIV”*.

None of this cuts any ice with the Wessely School and its members have long waged war against people with ME/CFS.

In 1990 Wessely wrote that ME exists *“only because well-meaning doctors have not learnt to deal effectively with suggestible patients”* (Psychological Medicine 1990:20:35-53); in 1991 he cited comments made by doctors between

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1880 and 1908 on patients with neurasthenia, with the very clear implication that such descriptions apply equally well to current ME patients: *“always ailing, seldom ill; a useless obnoxious element of society; purely mental cases; laziness, weakness of mind and supersensitiveness characterises them all; the terror of the busy physician”* (BMB 1991:47:4:919-941); in 1992 the Wessely School gave directions that in ME/CFS, the first duty of the doctor is to avoid legitimisation of symptoms (MRC Summary of CIBA Foundation Symposium on CFS, May 1992: ref: S 1528/1); in 1996 recommendations were made by Wessely et al in a Joint Royal Colleges Report (CR54) that no investigations should be performed to confirm the diagnosis and in 1999, Professor Michael Sharpe said in a lecture at Strathclyde University: *“Purchasers and Health Care providers with hard pressed budgets are understandably reluctant to spend money on patients...for whom there is controversy about the ‘reality’ of their condition (and who) are in this sense undeserving of treatment...Those who cannot be fitted into a scheme of objective bodily illness yet refuse to be placed into and accept the stigma of mental illness remain the undeserving sick of our society and our health service.”*

In October 2003, in a frenzied attack on people with ME and on those scientists and clinicians who regard it as an organic disorder, Wessely asserted that those who disagree with him and believe ME to be an organic disorder (to whom he referred as *“the radicals”*) are *“crazy”* and that they are *“engaged in fantasies, lies and gross distortions”*. He wrote that the *“radicals”* are left *“fighting yesterday’s battles”* (seemingly because he believes he has established that ME does not exist except as a false illness belief), that they need a *“reality check”* and that *“their behaviour is outrageous”* (private communication; available to Medical Defence Union lawyers on request).

Wessely’s dismissal of the biomedical evidence on ME/CFS has continued unabated, even though there is substantial evidence of pathology affecting the central and autonomic nervous systems, the immune system and the cardiovascular, endocrine, gastro-intestinal and musculoskeletal systems. Coroners’ reports confirm that people die from ME/CFS and published evidence shows that people with ME/CFS die 20 years prematurely.

At a medical meeting in March 2013 held in Bristol, Wessely informed attendees that ME has been caused almost entirely by the *“shockingly”* negative way in which some ME charities, in particular the ME Association, portray it as a viral illness, saying that this has harmed patients as it encourages them to focus too much on symptoms and to be fearful of activity, resulting in a vicious cycle of deconditioning. Making no distinction between chronic *“fatigue”* and ME/CFS, doctors were informed by Wessely that all patients with CFS would benefit from the same management regime, namely behavioural therapy and exercise (Research in Chronic Fatigue Syndrome – ups and downs; Bristol Medico-Chirurgical Society; 13th March 2013: approved for Continuing Medical Education).

Professor Wessely was intrinsically involved with the PACE trial and the three Principal Investigators (Professor Peter White, Michael Sharpe and Trudie Chalder) all work for the permanent health insurance industry.

Key areas of concern about the PACE Trial

After some years of unsuccessful attempts by Wessely’s close colleague, psychiatrist Professor Peter White (Chief Principal Investigator), the PACE trial started in 2004 and cost UK taxpayers £5 million. *“PACE”* is the acronym for **P**acing, **A**ctivity, and **C**ognitive behavioural therapy, a randomised **E**valuation, interventions that, according to one of the Principal Investigators, are without theoretical foundation.

The PACE trial was predicated on the Investigators’ belief that patients with ME/CFS must restructure their thought processes so that they no longer think they are physically sick; this was to be achieved by directive (as opposed to supportive) cognitive behavioural therapy (CBT, based on the illness model of fear avoidance) and by incremental aerobic graded exercise therapy (GET, based on the illness model of both deconditioning and exercise avoidance). No mention whatsoever was made of the well-documented underlying biomedical pathophysiology.

Both the Department for Work and Pensions (DWP) and the insurance industry took a keen interest in the PACE trial. It was the only clinical trial ever funded by the DWP and it did so because its then Chief Medical Advisor, Dr (now Professor Sir) Mansel Aylward, who works closely with the insurance industry, was assured by Professor White (who was lead advisor to the DWP on CFS) that it would remove people with ME/CFS from claiming benefits. This was effectively confirmed by the MRC by letter on 17th March 2011. In 2002 a book entitled *“Work and Mental Health: An Employers’ Guide”* was published by the Royal College of Psychiatrists Publications; it was co-edited by Dr Maurice Lipsedge, a psychiatrist who, like Professor Michael Sharpe, worked for the insurance industry. The book was sponsored by the massive re-insurance company Swiss Re (UK) plc for which Professor Peter White was Chief Medical Officer. In his contributed chapter, Professor Sharpe stated about ME/CFS:

“Prognosis is worse for patients who have a conviction that the cause is purely ‘physical’....CBT places particular emphasis on helping patients to reappraise their illness beliefs.....Refusal to accept appropriate treatment by the National Health Service and misleading advice are common problems”.

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Reappraising participants' illness beliefs by means of "cognitive restructuring" (aka "brain washing") was the ethos of the PACE trial.

The PACE trial is believed to be the first and only clinical trial that patients and the charities which support them tried to stop before a single patient could be recruited. **This was because the premise upon which the trial was predicated (the Investigators' belief that ME/CFS is perpetuated by psychological and behavioural factors and by faulty cognitions, activity avoidance and "hypervigilance to normal bodily sensations") had already been invalidated by the considerable body of evidence-based biomedical research on ME/CFS, hence the PACE trial should never have taken place.**

To international consternation, the Medical Research Council allowed the PACE trial to proceed as if this substantive body of mainstream knowledge did not exist, which was intellectually dishonest: a key principle of clinical research on human subjects is that it should build on foundations of existing knowledge about the disorder being studied, but in the case of the PACE trial, the biomedical evidence-base was simply air-brushed out of existence by the Investigators and those who supported them.

Specific concerns

Detailed analyses of the many failings of the PACE trial -- with full references -- can be found at <http://www.meactionuk.org.uk/magical-medicine.htm> and at <http://www.meactionuk.org.uk/COMPLAINT-to-Lancet-re-PAACE.htm> and at <http://www.meactionuk.org.uk/Normal-fatigue.htm> and at www.investinme.org/Article435StatisticsandME.htm

Failure to fully declare competing interests

Although some of the Principal Investigators' (PIs) competing interests were briefly mentioned in The Lancet article when selective results of the PACE trial were published in February 2011, trial participants were not initially made aware of the substantial competing financial interests of all three Principal Investigators (ie. their work for the insurance industry and for the DWP which co-funded the trial).

As well as being Chief Medical Officer for Swiss Re, the Chief Principal Investigator, Professor Peter White, was also Chief Medical Officer for Scottish Provident, an insurance company with a record of not paying legitimate permanent health insurance (PHI) claims to those with ME.

The insurance companies known to be involved in ME/CFS claims include UNUM, Swiss Life, Canada Life, Norwich Union (now Aviva), Allied Dunbar, Sun Alliance, Skandia, Zurich Life and Permanent Insurance, and as re-insurers, the massive Swiss Re (not the same as Swiss Life). These insurance companies all seem to be involved in re-insurance; for example, Norwich Union (now Aviva) uses Swiss Re. There seem to be two ways in which permanent health policies are underwritten between insurers and re-insurers: either the insurers agree to pay claims up to a pre-determined cut-off limit, after which the re-insurer becomes liable, or else the insurer and the re-insurer agree from the outset to share the costs of a claim.

This means that there is little hope of an ME/CFS claimant succeeding in a PHI claim, because both the insurers and the re-insurers inter-refer claimants with ME/CFS to the same psychiatrists, a situation confirmed by written evidence.

In November 2006 senior Parliamentarians found Professor White's close financial involvement with the insurance industry *"to be an area for serious concern and recommends a full investigation by the appropriate standards body"* (http://erythos.com/gibsonenquiry/Docs/ME_Inquiry_Report.pdf). Those parliamentarians who expressed this concern included the former Chairman of a House of Commons Science and Technology Select Committee and former Dean of Biology; a member of the Home Affairs Select Committee; a Minister of State for the Environment; a former President of the Royal College of Physicians; the Deputy Speaker of the House of Lords, and a former Health Minister and Honorary Fellow of the Royal College of Physicians.

Seven years later, nothing has changed and the same group of doctors who work for the insurance industry continue to influence UK policy on ME/CFS.

Professor White also does paid and unpaid work for Universities, the UK Government, the United States Centres for Disease Control, and for legal claimants and defendants (BMC Health Services Research 2003:3:25), not all of which were declared in The Lancet article.

Professor White is in fact lead advisor on "CFS/ME" to the Department for Work and Pensions and was a prominent member of the group who re-wrote the chapter on it in the DWP's Disability Handbook used by Examining Medical Practitioners, by DWP decision-makers and by members of the Appeal Services Tribunals. It is the DWP's known intention

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to remove as many people as possible from state benefits, and to this end ME/CFS (or CFS/ME) is a specifically targeted disorder.

Another Principal Investigator in the PACE trial, Professor Michael Sharpe, is also deeply involved with the permanent health insurance industry, especially with UNUMProvident, whose track record is disturbing (see “The advent of UNUMProvident into the UK benefits system” <http://www.meactionuk.org.uk/magical-medicine.htm>). Professor Sharpe is known for his recommendation to insurers that claimants with ME/CFS should be subject to covert video surveillance.

Members of the Scottish Parliament wrote to Allied Dunbar, another insurance company with which Professor Sharpe is involved, about their concerns over his suitability to give an unbiased view when assessing people with ME/CFS. Professor Sharpe asked MSPs to withdraw their statements to Allied Dunbar about him but they refused to do so.

The third Principal Investigator in the PACE trial, Professor Trudie Chalder, is also involved with the insurance industry in far more depth than is apparent from her brief declaration in the “Conflicts of Interest” in The Lancet. Her academic (as distinct from her mental nursing) career seems to have been devoted to promoting the interests of the insurance industry. Indeed, at a Symposium on CFS entitled “Occupational Health Issues for Employers” held at the London Business School on 17th May 1995 (at which attendees were informed that ME/CFS has been called “*the malingerer’s excuse*”), Miss Chalder spoke on “*Management of CFS*”, which she said included increasing activity and returning to work, and on “*Selling the treatment to the patient*”, whilst Professor Michael Sharpe spoke on “*cognitive psychotherapy*” and Professor Simon Wessely spoke on “*The Facts and the Myths*” about ME/CFS.

A physiotherapist involved with the PACE trial, Jessica Bavinton, is also more deeply involved with the insurance industry that is apparent from her brief declaration in The Lancet; she was in fact the primary author of the PACE Trial Graded Exercise Therapy manual which, in the October 2007 Declaration of Interests for the NICE Guideline on CFS (CG53) she declared her intention to publish, an intention which placed her in the position of having a commercial interest in the outcome of the PACE Trial.

Miss Bavinton works for more than three PHI companies, one being Scottish Provident, whose claims handler Kenneth MacMahon by letter dated 7th August 2007 stated to a claimant: “*We are arranging for a claims visit. This will be done by Jessica Bavinton who specialises in performing home visits of this nature*”.

On 13th August 2007, in a (recorded) telephone conversation, Miss Bavinton herself stated that she does “*lots of these assessments for insurance companies*”.

Thus the PIs have a considerable interest in ensuring that ME/CFS is denied legitimacy as an organic disorder; if accepted as such, it would cost their insurance company paymasters (and the Government departments which they advise) an inordinate amount of money.

The Chair of the West Midlands Multicentre Research Ethics Committee (MREC) which granted ethical approval for the PACE trial (reference MREC/02/7/89), Dr Jammi Rao, went on record in 2002: “*Consent obtained on the basis of withholding information on an issue that patients consider important is not fully informed consent*” (BMJ 2002:325:36-37).

Failure to fully declare competing interests is in breach of section B22 of the Declaration of Helsinki 2000 (the version in force at the time of the PACE trial).

Failure to comply with professional ethical guidance and Codes of Practice

In the PACE Trial Protocol, the Investigators stated their intention to comply with certain codes of practice:

“The trial will be conducted in compliance with the Declaration of Helsinki, the trial protocol, MRC Good Clinical Practice (GCP) guidance, the Data Protection Act (1998), the Multi-centre Research Ethics Committee (MREC) and Local Research Ethics Committees (LREC) approvals and other regulatory requirements, as appropriate. The final trial publication will include all items recommended under CONSORT (Consolidated Standards of Reporting Trials)”.

Although not mentioned by the Investigators, the provisions of the General Medical Council Guidance Good Practice in Research and Consent to Research would also have applied, as would the provisions of the Department of Health Research Governance Framework for Health and Social Care, Second Edition, 2005; 2:3:1.

There appear to have been some notable failures to comply with the required ethical standards, for example:

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- it appears that the PACE trial did not conform to the Declaration of Helsinki in full: participants and others have confirmed in writing that coercion was used to compel people to enter the trial on threat of losing medical support for their State benefits (breaching A8 and B20); furthermore, coercion was said by participants to have been used to prevent them from withdrawing from the trial, and participants have provided written evidence of this
- medical research involving human subjects must be based on a thorough knowledge of the existing body of scientific literature, but the Investigators ignored the substantial biomedical evidence-base on ME (breaching B11) and the trial was predicated on the Investigators' firm belief that ME/CFS is not an organic disease but an aberrant illness belief. **Since the general body of knowledge known about by other clinicians and researchers working in the field of ME/CFS is now so great, the question repeatedly asked is: at what point will that body of scientific knowledge be so great that it will be considered serious professional misconduct to ignore it and to continue to deceive patients by pretending that it does not exist, as happened in the PACE trial?**
- the anticipated benefits of two of the interventions were greatly overplayed to participants in the CBT and GET groups but not to participants in the APT (pacing) or SSMC groups (standardised specialist medical care): those in the former two groups were repeatedly led to believe that they would be cured and could return to work, with therapists even offering to write to participants' employers to ensure that they would be returning to work, whilst those in the APT group received no such guarantee
- despite the Investigators' assurances of the strictest confidentiality, participants' data were not kept securely and were stolen from an unlocked drawer (Southwark police crime incident number 3010018-06 reported on 22nd March 2006); this was in breach of section B21. Affected participants were not made aware that confidential information about them had been stolen
- the Investigators already knew that CBT and GET do not work for ME/CFS patients: *"These interventions are not the answer to CFS"* (Editorial: Simon Wessely; JAMA 19th September 2001:286:11) and that *"many CFS patients, in specialised treatment centres and the wider world, do not benefit from these interventions"* (Huibers and Wessely; Psychological Medicine 2006:36:(7):895-900) (breaching B19)
- participants were not informed of the potential risks inherent in the trial, in particular they were not informed of the nature, degree, or duration of the discomfort or relapse they might reasonably be expected to experience through participating in aerobic exercise in the PACE Trial (breaching B22).

It appears that the Investigators likewise failed to observe necessary principles of good research required by the GMC "Good practice in research and Consent to research"

(http://www.gmc-uk.org/static/documents/content/Research_guidance_FINAL.pdf)

For example, the following requirements should have pertained but evidence abounds that they did not:

- paragraph 5: *"To protect participants and maintain public confidence in research, it is important that all research is conducted...with honesty and integrity"*
- paragraph 8: *"You must make sure that the safety, dignity and wellbeing of participants takes precedence over the development of treatments"*
- paragraph 9: *"You must be satisfied that the anticipated benefits to participants outweigh the foreseeable risks"*
- paragraph 13: *"You must keep your knowledge and skills up to date"*
- paragraph 17: *"You should make sure that any necessary safeguards are in place to protect anybody who may be vulnerable to pressure to take part in research"*
- paragraph 21: *"You must conduct research honestly"*
- paragraph 22: *"You must be open and honest with participants....You must answer questions honestly and as fully as possible"*
- paragraph 24: *"You must report research results accurately, objectively, promptly, and in a way that can be clearly understood. You must make sure that research reports ...do not contain false or misleading data"*

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- paragraph 27: “You must not allow your judgment about a research project to be influenced, or seen to be influenced, at any stage, by financial, personal, political or other external interests”
- paragraph 29: “You must make sure that...you respect their right to decline to take part in research and to withdraw from the research project at any time”
- paragraph 31: “You must...make sure that any data collected as part of a research project are stored securely”.

Written evidence exists of failures by the Investigators in all those domains.

The PACE Trial was jointly funded by the Department of Health, whose own Research Governance Framework for Health and Social Care, Second Edition, 2005, states:

“2.3.1: All existing sources of evidence...must be considered carefully before undertaking research”.

Without doubt, the Investigators were in breach of this important tenet of scientific research.

The Governance arrangements for NHS Research Ethics Committees, 2001, state:

*“9.8 The Research Governance Framework makes it clear that the sponsor (in this case the main sponsor was Barts and the London, Queen Mary School of Medicine and Dentistry, but ultimate responsibility rested with Professor Peter White) is responsible for ensuring the quality of the science. Paragraphs 2.3.1 and 2.3.2 state: **It is essential that existing sources of evidence, especially systematic reviews, are considered carefully prior to undertaking research. Research which duplicates other work unnecessarily or which is not of sufficient quality to contribute something useful to existing knowledge is in itself unethical**”.*

As noted above, the Investigators already knew from previous published research that CBT and GET are not the answer to ME/CFS.

Some important concerns relating to the Investigators’ failures to comply with the above ethical requirements include the following:

- participants were intentionally misinformed about the nature of ME/CFS; they were informed that their symptoms were not the result of any pathological process and they were disabused of their correct belief that ME/CFS is an organic illness
- potential participants were assured that they would be receiving “specialist medical care” from “clinic doctors experienced in the assessment and treatment of CFS/ME”, which implied that participation in the PACE Trial would afford them specialist medical care that was not available elsewhere. This was untrue: participants receiving SSMC alone may have seen the Fatigue Service clinic doctor only three times for 30 minutes each time during their participation in the trial, a total of 90 minutes throughout the trial, which does not constitute “specialist medical care”; furthermore, the SMC arm of the PACE Trial used 27 liaison psychiatrists (of whom 22 were from the same centre). Of the liaison psychiatrists, only 4 of the 27 had completed their training, the remaining 23 were trainees. “Trainees” cannot be considered to be knowledgeable “medical specialists” experienced in the care of people with ME/CFS, so participants were deceived. Furthermore, one of the “specialist medical care doctors” was named in The Lancet article as being Simon Wessely, who believes that ME does not exist except as an aberrant belief that one has an illness called ME
- participants were seriously misled about one of the arms of the trial, Adaptive Pacing Therapy (APT). They were led to believe they were entering a trial testing the efficacy of pacing; this was untrue, so they may thus not have been in a position to give fully informed consent. All three Principal Investigators are known to be strongly opposed to pacing (BMJ 5th January 2002:324:7; BMJ 19th January 2002:324:131) and the Chief PI, Professor White, has publicly admitted conflicts of interest about it (Postgraduate Medical Journal 2002:78:445-446). For all three PACE trial PIs to have publicly-known conflicts of interest about one of the interventions being tested in the trial and to be strongly opposed to that intervention may cast doubt on the validity of their finding that pacing does not work. It is therefore necessary to be aware that the APT used in the PACE Trial is very different from pacing as practiced by patients with ME/CFS. APT as used in the PACE Trial was a vehicle for incremental aerobic exercise and it involved planning, achieving and sustaining targets. The APT Therapists’ Manual listed requirements for APT including “**plan set activity in advance**” (so activity had to be “**set activity**”, not simply what the patient might have been capable of doing at the time); there was to be “**activity analysis**”; APT participants had to “**constantly review model, diaries and activity**” and there was the requirement to “**involve relatives**”, which is nothing like pacing, ie. “doing what you can when you can”. The Lancet article seriously misled readers because the authors stated: “**Our results do not support pacing, in the form of APT, as a first-line**

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therapy for chronic fatigue syndrome". From his published record, Professor White was never going to support pacing, but it is improper to refer to APT used in the PACE Trial as "pacing"; the two are not the same, and other impeccable research (for example, Leonard Jason et al; AAOHN May 2008:56:5) has found pacing to be beneficial for people with ME/CFS.

- participants in two of the four groups were informed that "recovery" was possible with those interventions: CBT and GET were promoted as "curative" during the life of the PACE trial. It is a basic rule of any clinical trial that participants are not told during the trial how effective is the intervention that they are receiving, but this was not complied with in the PACE trial: participants in the CBT group were informed on five separate occasions in their own CBT Manual that they could "**overcome their CFS/ME**" (ie. they could expect to be cured) by the application of CBT. **It should never be suggested to participants in a clinical trial that the intervention they are undertaking is a cure unless it is certain that it is indeed curative, in which case there would be no need for a clinical trial to prove the efficacy of the intervention.** To mislead participants in a clinical trial by suggesting that a cure can be expected when there is no such certainty is in breach of the General Medical Council Regulations as set out in "Good Medical Practice" (2006): "*You must not make unjustifiable claims about the quality or outcomes of your services in any information you provide to patients. It must not offer guarantees of cures, nor exploit patients' vulnerability or lack of medical knowledge*". To have informed selected PACE participants -- via the Trial manuals and therapists' instructions -- that they could "recover" with two of the four interventions being tested (ie. those in the CBT and GET groups), whilst APT participants were not given such advice, appears to have been seeking to bias the outcome in favour of the Investigators' favoured interventions which, if successful, would have supported their belief in a psycho-social model of ME/CFS.
- any medical advice given to participants had to be "*compatible with any therapy that the participant is receiving (APT, CBT, GET or SSMC alone)*". Thus the doctor delivering Standardised Specialist Medical Care (which amounted to little more than a "Fatigue Service" clinic doctor -- often a trainee psychiatrist from King's College Hospital -- handing out a leaflet and giving general advice about balancing activity and rest and offering antidepressants) had to give medical advice based not on their clinical assessment or a participant's medical need but in accordance with whatever "therapy" the participant was receiving: ie. if the participant was receiving GET and experienced an exacerbation of symptoms, the doctor had to reassure the participant that this was a normal consequence of using deconditioned muscles. If, however, the participant was in the APT arm of the trial and experienced the same symptoms, the doctor had to tell the participant that they were doing too much and should rest more; **thus participants in the same clinical trial with identical symptoms were to be given differing advice by a clinician that was solely dependent on the particular arm of the trial to which they had been allocated.** The Minutes of the Joint meeting of Trial Steering Committee and Data Monitoring and Ethics Committee held on 27th September 2004 record: "*clinic doctors would be working within a remit of advice and medication they could give*", a situation that many people deemed unethical.

It cannot be reiterated enough that many people – including not just patients with ME/CFS and their families, but international academics, medical scientists and clinicians who have kept abreast of the biomedical developments in ME/CFS – are deeply dismayed by the apparent abuse of the scientific process that appears to have been condoned and perpetrated by the Medical Research Council, the Principal Investigators and indeed by all those involved with the PACE trial. It is irrefutable that the Wessely School's beliefs about ME/CFS appear not to have advanced with the progression of medical science over the last 25 years.

The chosen entry criteria

The Investigators used entry criteria for the PACE trial that did not define the population they purported to be studying: they used their own "Oxford" criteria, in which the Chief Principal Investigator had a financial interest, as he co-funded them himself. The Oxford criteria have neither the appropriate degree of sensitivity to identify those with ME, nor the specificity to separate them from the wider "fatigued" population; moreover, the Oxford criteria specifically exclude those with a neurological disorder (and ME is classified as a neurological disorder by the WHO) but the Investigators: "*chose these broad criteria in order to enhance generalisability and recruitment*" (Trial Identifier section 3.6).

On 12th May 2004 a Minister of State, Dr Stephen Ladyman MP, confirmed to an All Party Parliamentary Group that GPs were being offered financial inducements to send people who did not suffer from ME/CFS into the PACE trial.

The use of a heterogeneous population by deliberately including patients who do not have the disorder in question contravenes elementary rules of scientific procedure.

Failure to subgroup the cohort

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The Investigators maintained that there would be a secondary analysis using the “London criteria”. It is a straightforward fact that if those with a classified neurological disorder were excluded from the outset by strict adherence to the Oxford entry criteria, no amount of “secondary analysis” would reveal those with a classified neurological disorder.

Whilst initially confirming their intention to use the “London criteria” for ME as set out by the late Dr Melvin Ramsay (which required neurological disturbance to be present), sometime between March 2003 and October 2004 the Investigators decided to abandon this and to adopt their own version of the “London criteria”.

In contrast to the original Ramsay definition, the Investigators’ own version does not require the presence of any neurological disturbance, and this lessened the distinction between true ME and “medically unexplained fatigue” (a somatisation disorder), which accorded with the Investigators’ known beliefs and was thus to their advantage.

Even more disturbing is the fact that in the Investigators’ own version of the “London criteria”, there was no requirement for the pathognomonic symptom of ME (post-exertional exhaustion and malaise) to be present.

All that was left were essentially the Oxford criteria (but with the absence of depression or anxiety), which was an entirely inadequate description of the neurological disease ME.

It is notable that in a trial purporting to be studying ME/CFS and despite apparently screening for psychiatric disorders, the authors reported a 47% prevalence of mood and anxiety disorders at baseline, with a near equivalent use of antidepressants (41%). A 47% prevalence of mood and anxiety disorders in ME/CFS is not compatible with results published by others.

Research has found that rates of depression in ME/CFS are no higher than in other chronic medical conditions (Shanks MF et al; Brit J Psychiat 1995:166:798-801) and that the rates of overall psychiatric disorders are no higher than general community estimates (Hickie I et al; Brit J Psychiat 1990:156:534-540).

Not a Randomised Controlled Trial as claimed

Although the trial documentation refers to it as an RCT (randomised controlled trial), it was not a controlled trial.

Biases

Known biases may not have been avoided; for example, the assessors knew to which of the intervention groups the participants had been allocated in the trial, such masking being deemed “*impractical*” by the Investigators.

The PACE Trial Manuals

The Manuals used in the PACE trial show that the authors either ignored or did not understand medical science; they were ill-written, often grammatically incorrect, heavily biased towards the Investigators’ own beliefs about the nature of ME/CFS (in that no mention was made of the published biomedical underpinnings), lacking in intellectual rigour and were internally inconsistent.

They contained many contradictory claims, for example, they stated that therapists would be treating people “*who generally do too much*” whilst also stating that the PACE trial was based on “*the illness model of both deconditioning and exercise avoidance*” without explaining how people who do too much also suffer from exercise phobia and are deconditioned as a consequence. The manuals recommended going to the pub for a drink as a form of approved recreational activity, whilst also stating that participants’ symptoms are exacerbated by alcohol. A “*medical specialist*” in one sentence became a “*therapist*” in the next sentence.

More importantly, the manuals included advice that cannot be considered ethical by any independent and reasonable observer: participants were told to ignore symptoms because they do not result from physical disease: indeed one of the manuals taught therapists how to manage participants who believed they had a physical disease and how to persuade them that this was not the case and to dissuade them from seeking further medical attention. It hardly needs reiterating that patients die from ME.

Therapists were trained not to be honest with participants in that they were to assure participants that they believed ME/CFS to be a “real” (ie. “organic”) disease when in fact therapists were taught that it was not an organic disorder but a behavioural disorder.

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Speculation was portrayed as fact and assumptions were portrayed as evidence.

A “warm” and “empathetic therapeutic relationship” between therapist and participant was to be created even though it was not authentic, so participants were deliberately deceived. This contrived “empathetic” alliance was designed to undermine the self-confidence of participants, who were instructed by the therapist (who by displaying “empathy” thus gained the trust of participants) not to listen to their own bodies; participants were to be repeatedly told that they had thinking errors and that their “negative thought patterns” must be challenged; they were to be persuaded that they were not physically ill; that their life-style caused their illness and that the way they managed their illness had prevented them from recovering.

There is no evidence to show that the many pathophysiological abnormalities that have been demonstrated in ME/CFS are caused by wrong illness beliefs or behaviour; on the contrary, there is a significant peer-reviewed evidence-base demonstrating that ME/CFS is a serious, organic, chronic, multi-system disorder.

Failure to adhere to the published protocol

The Investigators failed to adhere to their published protocol and changed it on numerous occasions once the trial was under way.

This means that they did not report their results according to their original protocol, which is very bad science indeed, as it means their conclusions are not reliable.

Professor White claims that it is common practice to amend a protocol as a trial goes along, but that is not true.

Dr Ben Goldacre of “Bad Science” says of such practice: “in a trial... you have to say which is the ‘primary outcome’ before you start: you can’t change your mind about what you’re counting as your main outcome.... It’s not just dodgy, it also messes with the statisticsYou cannot change the rules after the game has started. You cannot even be seen to do that” (The data belong to the people who gave it to you: The Guardian: 5th January 2008). The fact is that the PACE Investigators did change the rules after the game had started and they have been seen to do that.

Change of entry score once the trial was underway

Eleven months after the trial began, the Investigators changed the entry score on the short form-36 physical function subscale (SF-36 PF) rating from 60 to 65. This was said to be to improve recruitment, which was a problem, but it meant that the trial included people with better physical functioning scores at baseline than those recruited at the outset.

It is a most unusual situation in any clinical trial for the first tranche of participants to meet different entry criteria from those who were recruited after a trial has started.

This particular change was of key significance in that scores recorded on this same scale played a vital role in assessing outcomes, as people who had higher scores on this scale at baseline required less change during the course of the trial to attain a relatively higher score on completion. They may also have been less ill and therefore better able to engage with CBT and exercise than people who attained lower physical function scores at the outset.

Objective measures of outcome were dropped

The key objective measure of outcome was dropped: the Investigators originally intended to obtain a non-invasive objective measure of outcome using post-treatment actigraphy (and obtained ethical approval and funding on this basis) but once the trial was under way the Investigators abandoned actigraphy entirely and relied largely on participants’ subjective responses to questionnaires, which are notoriously unreliable.

To rely on subjective data in a trial that intentionally set out to modify participants’ own subjective beliefs cannot be classed as a scientific study.

A significant point is that the Investigators measured subjective changes in participants who suffer from what the Wessely School refer to as “perceived disability” (BMJ 2003:326:595-597). This means that on the one hand, the Wessely School believe that people with “CFS/ME” are unreliable in their own assessment of their disability (because the Wessely School assert that people with ME/CFS only “perceive” themselves to be ill and that they hold “aberrant illness beliefs”),

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yet on the other hand the Wessely School based the outcome of a £5 million study on such patients' personal assessment of their disability (ie. PACE Trial participants were deemed capable of accurately reporting their symptoms/disability).

In other words, the Investigators were satisfied that the only requirement to prove that CBT and GET are effective was for participants (whose judgment the Investigators regard as suspect) to say that they are effective.

Changes in scoring methods

Changes in scoring of participants' self-reported measures of fatigue were also not reported as per the protocol: when post-intervention changes are so small, they do not register on the scale originally chosen by the Investigators, so the Investigators introduced a different scoring method which enabled them to show a small statistical (but not clinical) improvement.

The six minute walking test (6MWT)

A secondary outcome measure was the 6 minute walking distance test (6MWT). In their protocol, the Investigators stated: *"The six-minute walking test will give an objective measure of physical capacity"* and they cited the American Thoracic Society's 2002 guidelines: *"The walking course must be 30 metres in length"*.

The ability of such a test to assess capacity in ME/CFS is highly debatable, as it fails to take into account the cardinal feature of ME/CFS (post-exertional fatigability and malaise).

The Chief Principal Investigator himself has published evidence supporting the need for serial post-exercise testing in ME/CFS (JCFS 2004:12:(2):51-66) but that did not happen in the PACE trial; even though one of the cited references (BMJ 1982:284:1607-1608) stipulates that the 6MWT needs to be carried out twice to achieve reproducible results, the Investigators did not do so and provided no credible reason for not incorporating repeat testing in the trial design.

Further, the 6MWT is known to have low test-retest reliability (even more so in this case, as the assessors were not blinded and knew to which of the intervention groups participants had been allocated).

The results of the 6MWT were dismal: the mean (ie. average) distance recorded by those who had undergone CBT was 354 metres and for those who had undergone GET the mean distance was 379 metres, the latter being only a 67-metre increase from baseline after one year's therapy.

These scores were lower than scores documented in many other serious diseases, such as those awaiting lung transplantation (where a six minute walking test of less than 400 metres is regarded as a marker for placing a patient on the transplant list) and the mean score of those in class III heart failure is 402 metres.

PACE trial participants (whose average age was 38) did not achieve a mean six minute walking distance of 518 metres, a level considered abnormal for healthy people aged 50-85 years.

If PACE participants could not achieve a one-off result achievable by healthy people of 85, then there is little hope that they can function adequately in real life and the Investigators' proclamations of "recovery" are insupportable.

Moreover, data on the 6MWT were available for only 69% - 76% of participants, a completion figure roughly 20% lower than for the other secondary outcome measures, for which the Investigators offer no explanation.

Significantly, the CBT group managed less of an average increase in walking distance than those in the SMC alone group.

The Chief Principal Investigator has attempted to justify such poor results by blaming the short length of the corridor used to carry out the test, which was only 10 metres (not the required 30 metres): conceding that there was a need for a greater number of turns than was usual, he said that, because of concern for participants, they were not given encouragement to walk faster.

It is possible that the Chief Investigator chose not to repeat the 6MWT in light of the UK Chief Medical Officer's Working Group Report of 2002 (from whose expert group he and Trudie Chalder walked out when it became clear that they were not going to achieve their aim of definitively categorising ME/CFS as a behavioural disorder); that report was clear: ***"Perhaps the prime indicator of the condition is the way in which symptoms behave after activity is increased beyond what the patient can tolerate. Such activity...has a characteristically delayed impact"***. This being so, the results of a re-test were likely to have been even worse.

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The results of the 6MWT are significant and cannot be explained away as the Investigators have attempted to do by claiming that: *“recovery from chronic fatigue syndrome (CFS), which is defined by a patient’s reported symptoms, is arguably best measured by multiple patient-reported outcome measures, rather than a single performance test”* (<http://www.meassociation.org.uk/2013/07/pace-trial-letters-and-reply-journal-of-psychological-medicine-august-2013/>).

Such views are at variance with other international researchers’ findings in ME/CFS, who have demonstrated that patients’ subjective reports do not correlate well with objective measures of activity.

Such views are also at variance with the Investigators’ own published views: *“Objective measures of physical activity have been found previously to correlate poorly with self-reported outcomes”* (Psychological Medicine 2013: Oct; 43(10):2227-35; Epub ahead of print).

The 6MWT was the only allegedly “objective” outcome measure and it showed that the PACE trial interventions CBT and GET were not effective in the cohort studied.

Furthermore, the PACE Trial walking test gave no indication for how long participants could maintain the walking speed beyond the 6 minute test, nor if they suffered from post-exertional exhaustion, nor any indication of participants’ walking ability over a longer time frame, or if they experienced exacerbation of other symptoms.

Changes to the “positive outcome” score

Initially the Investigators decided in 2002 that an SF-36 physical function (SF-36 PF) score of 75 would indicate a “positive outcome” (which is not the same as “recovery”); in 2006 this was lowered to 70 but after the trial had finished, the Investigators dropped their “positive outcome” analysis altogether.

The Investigators’ chosen “normal range” for their *post-hoc* analysis

The Investigators’ deviation from the protocol in terms of entry scores meant that ratings which would qualify a person as being sufficiently impaired to enter the trial overlapped with those considered “within the normal range” when assessed on completion of the trial.

The illogical situation whereby participants could score worse on completion than on entry but still be classed as being within the “normal range” as a result of the alleged efficacy of the interventions arose because of the Investigators’ *post-hoc* changes, revisions and re-calculations and their failure to use the benchmarks to which they had committed themselves in the protocol.

Changes were made by the Investigators in their reference material on which they relied for a comparative group for their “normal range”; in fact they used a highly questionable comparison group to obtain their “normal range” for use in the PACE trial.

In his application dated 12th September 2002 to the West Midlands Multicentre Ethics Committee (MREC) seeking permission to amend the approved protocol, Professor White described the derivation of his new threshold of “normal” as follows: *“We will count a score of 75 [out of a maximum of 100] or more as indicating normal function, this score being one standard deviation below the mean score [90] for the UK working age population”*, citing Jenkinson C et al (BMJ:1993:306:1437-1440) and this paper was cited in the trial protocol references.

However, in their Lancet article the Investigators made no mention of that paper; instead they relied on Bowling et al (J Publ Health Med 1999:21:255-270) as the source of their “normal range”, citing a mean (ie. average) for the UK working age population of an SF-36 PF score of 84 with an SD (standard deviation) of 24, making 60 the threshold of their chosen “normal range” for the PACE trial (although Bowling et al do not use the term “normal range”).

The “normal range” is not the same as “normal” function as generally understood; the former is a statistical concept whereas in lay terms the latter implies high physical function with no impairment.

In statistical terms, the “normal range” is the mean plus/minus one standard deviation from the mean; when data is equally distributed round a mean, the concept relates well to what is the norm. However, health in the general population is not normally distributed around a mean but skewed towards the top end of the scale – a fact to which Bowling et al drew specific attention. In other words, good health is the norm and it is not possible to be above the range of normal on the SF-36 physical function subscale.

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The Investigators' chosen threshold for their "normal range" fails to deliver a meaningful indication of PACE participants' physical function; it was unduly low in relation to physical function and requires scrutiny.

In their Lancet article the Investigators describe their comparison group as being the working age population but the data set analysed by Bowling et al on which the investigators rely relates to the adult population as a whole, not the working age population, and the adult population includes elderly adults (in fact it included everyone aged between 16 and 85+), thus lowering the threshold of the "normal range" and thereby boosting the proportion of PACE participants who could be deemed to have improved on conclusion of the trial.

When this was pointed out to him, the Chief Principal Investigator had no option but to acknowledge that: *"We did, however, make a descriptive error in referring to the sample we referred to in the paper as a 'UK working age population', whereas it should have read 'English adult population'".* Even so, this was an inappropriate comparator to have used in relation to PACE trial participants (whose average age, as noted, was 38).

Any source that relates to the general population as a whole will include those who are beyond working age, the very old, and the chronically or short-term sick. The appropriate comparison group for PACE participants should have been the SF-36 physical function scores for age and sex-matched healthy adults of working age.

If the threshold of the Investigators' "normal range" were to have been set any higher, it would have been more difficult – if not impossible – for them to claim even moderate success for the PACE trial.

Turning to the other primary outcome measure (the fatigue score), a participant could have entered the PACE trial with a bimodal fatigue score of 6 and left the trial with a score of 7, 8 or 9 (ie. with greater fatigue) yet still fall within the Investigators' own *post-hoc* "normal range".

Because on 17th February 2011 some PACE participants' achievement of the Investigators chosen "normal range" was presented to the media (and hence to the public) as equating to "normal" by one of the Investigators (Professor Trudie Chalder) at the Science Media Centre press briefing on the PACE trial results, this was interpreted as "recovery". This was not surprising, as her words were: *"Twice as many people on graded exercise therapy and cognitive behaviour therapy got back to normal"*.

This was widely reported by the media the following day; for example, The Guardian's health correspondent proclaimed: *"More people recover if they are helped to try to do more than they think they can"* (18th February 2011). Other newspapers and outlets followed suit: *"Got ME? Just get out and exercise, say scientists"* (The Independent); *"Got ME? Fatigued patients who go out and exercise have best hope of recovery, finds study. Scientists have found encouraging people with ME to push themselves to their limits gives the best hope of recovery"* (Daily Mail); *"Exercise and therapy can reverse effects of ME"* (The Daily Record); online medical sources such as NHS Choices and NHS Evidence also exaggerated the reports of a successful outcome, as did The Lancet.

Because of numerous complaints about the misrepresentation of "recovery" in the media and the medical press, the Investigators were obliged to write to The Lancet confirming that: *"Being within a 'normal range' is not necessarily the same as being recovered"*, but the harm had been done.

In the same issue as the Investigators' article, The Lancet carried a Comment by two Dutch clinical psychologists, Professors Gijs Bleijenberg and Hans Knoop, with both of whom Professor White had previously co-authored published papers on "CFS"; indeed, Gijs Bleijenberg was one of the authors of a manual on which the PACE trial's own CBT manual was based. Bleijenberg and Knoop claimed – erroneously – that: *"PACE used a strict criterion for recovery: a score on both fatigue and physical function within the range of the mean plus (or minus) one standard deviation of a healthy person's score. In accordance with this criterion, the recovery rate of cognitive behaviour therapy and graded exercise therapy was about 30%".* This was blatantly wrong, because not only did the Investigators not use a "healthy person's score" as a comparator, but no recovery figures had been published.

It has been confirmed by The Lancet that Professor Peter White himself had been shown the Dutch authors' Comment before publication and had approved it for publication; it was unquestionably wrong, so it is unclear why he approved it unless he badly wanted the message of "30% recovery" to hit the medical headlines as well as the media.

The Lancet was subsequently admonished by the Press Complaints Commission (PCC) for failing to take care not to publish inaccurate or misleading information and for breaching Clause 1 (Accuracy) of the Editors' Code of Practice. The PCC adjudication said that Bleijenberg and Knoop had *"failed to make clear that the 30 per cent figure for "recovery" reflected their view that function within "normal range" was an appropriate way of "operationalising" recovery – rather than statistical analysis by the researchers based on the definition for recovery provided. This was a distinction of significance, particularly in the context of a comment on a clinical trial published in a medical journal"*.

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Having shamefully misrepresented the successful outcome of the PACE trial at its press briefing, the Science Media Centre – which claims to promote accurate coverage of science -- did not ensure that this was reported in the media; furthermore, the reason that the Countess of Mar had to resort to the Press Complaints Commission was that The Lancet, having at first acknowledged in writing that it would have to correct the error in the Comment, repeatedly refused to do so after consultation with Professor White.

“Recovery” scores

As noted, the “normal range” does not equate with “normal” health and it certainly does not equate with “recovery” from ME/CFS.

In the Investigators’ original definition of “recovery” as set out in their protocol, a participant had to achieve a score of 85 or above on the SF-36 physical function subscale; however, when selective results of the trial were published in The Lancet and Psychological Medicine, the Investigators chose to abandon the statistical analysis set out in the trial’s protocol and instead constructed a set of *post-hoc* metrics by which the success of the interventions were to be assessed.

The *post-hoc* metric for physical function warrants close scrutiny because its derivation contains a significant statistical error and its description in both journals is misleading.

In Psychological Medicine White et al wrote: *“We changed our original protocol’s threshold score for being within a normal range on this measure from a score of ≥ 85 to a lower score as that threshold would mean that approximately half the general working age population would fall outside the normal range. The mean (SD) scores for a demographically representative English adult population were 86.3 (22.5) for males and 81.8 (25.7) for females (Bowling et al 1999). We derived a mean (SD) score of 84 (24) for the whole sample, giving a normal range of 60 or above for physical function”* (Psychological Medicine 2013: Oct; 43(10):2227-35: Epub ahead of print).

This statement proved to be inaccurate.

It is clear that from the start of the trial Professor White et al had two distinct concepts in mind: “positive outcome” (defined as the mean SF-36 PF score minus 1 SD or above) and “recovery” (a higher threshold defined as an SF-36 PF score of 85 or above).

It is instructive to note the progressive widening of these thresholds over time:

Year	Source	Mean minus 1 SD	Positive Outcome	Recovery
2002	Trial protocol	75 [1]	75	not specified
2007	Trial protocol	70 [2]	75	≥ 85
2011	Lancet	60	60	not specified
2013	Psych Med	60	≥ 60	≥ 60

[1] 2002: *“We will count a score of 75 [out of a maximum of 100] or more as indicating normal function, this score being one standard deviation below the mean score [90] for the UK working age population”*

[2] 2007: *“A score of 70 is about one standard deviation below the mean score (about 85, depending on the study) for the UK adult population”.*

Therefore it can be seen that between 2002 and 2011-2013 the Investigators’ derivation of the mean SF-36 PF score minus 1SD fell from a score of 75 or above to a score of 60 or above. Similarly, their definition of recovery fell from a score of 85 or above to a score of only 60 or above.

Consequently, by publication, there was no difference between a positive outcome and recovery, both of which fell under the common rubric of the Investigators’ chosen “normal range”.

Not only do the published results lack conceptual clarity, they also contain an important statistical error. The Investigators’ stated justification for reducing the SF-36 physical function threshold of the “normal range” from 85 to 60 (namely that approximately half the general working age population would fall below an SF-36 physical function threshold of 85) is not supported by any cited reference and specifically not by Bowling et al, although it appears possible that the Investigators intended readers to assume that they were relying Bowling et al for that statement.

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Independent re-analysis of Bowling's raw data shows that just 18% (not approximately 50% as claimed by the PACE Investigators) fall below an SF-36 physical function threshold of 85, and once those with long-term health issues are excluded, the figure falls to 8%. These figures are nowhere near the figure of approximately 50% upon which the Investigators relied. In fact, at least half the UK working age population have an SF-36 physical function score of 100 according to Bowling et al.

This vitiates the Investigators' stated reason for lowering the score from 85 to 60 and consequently invalidates the conclusion of their published paper on "recovery" (Psychological Medicine 2013: Oct; 43(10):2227-35: Epub ahead of print).

The Investigators did not use normalised scoring of the SF-36 physical function subscale; instead, they asked ten questions, each scoring a maximum of ten points, so the maximum score for someone reporting no physical disability was 100. The Investigators claim that, when scored in this way, and apparently relying on Bowling et al, a PACE participant could be described as recovered if they had a score of 60 or above out of 100.

The new threshold of 60 is noteworthy because it is lower than the score of 65 required for entry to the trial, so a participant could deteriorate or stay the same but still be counted as recovered in the published results.

This has resulted in an explicit contradiction by the Investigators because, having set the lower bound for recovery at 60, they also state in the same paper that any SF-36 score of less than or equal to 65 represents abnormal physical function, therefore, in the same paper, scores of 60 and 65 represent both abnormal physical function and recovery.

This is not just a theoretical concern, as an FOIA request revealed that nearly 13% of participants had scores of 60 or 65 when they entered the trial: if 13% entered the trial with "normal" function, why were they treated?

When the Investigators' paper on "recovery" was published in January 2013 in Psychological Medicine, the internet was awash with incredulity, for example:

- *"I wonder how this got through peer review"*
- *"If you look at the distribution plot in Bowling they are not Gaussian (a Gaussian graph is typically bell-shaped) and hence SD (standard deviation) is meaningless anyway, so (they) shouldn't be allowed to use it to generate (their) threshold. How can a senior statistician from the MRC get things so very wrong?"*
- *"The degree of scientific and mathematical illiteracy...is appalling. The most basic stuff we teach in General Science to teenagers seems to be lacking...don't draw conclusions beyond your data, and most basic of all, opinions are not fact. I don't even want to go into their abuse, misuse and general ignorance about statistical analysis of data"*
- *"White et al stated in their recent response...that changes to the trial protocol were approved independently by two trial oversight committees....It would be rather concerning if such a basic error managed to pass three groups of professionals involved with the PACE trial, not to mention being unspotted by multiple peer-reviewers in at least two journals, including The Lancet, after what its editor in chief described as 'endless rounds of peer review'".*

It is important to be aware that the figure of 60 for "recovery" was used by the Investigators specifically for the PACE trial and it contradicts how they themselves previously defined markers of recovery in the same disorder using the same measure: in 2007 they stated: "A patient had to score 80 or higher to be considered as recovered" (Psychother Psychosom 2007;76:171-176) and in 2009 their Dutch colleagues asserted: "A cut-off of less than or equal to 65 was considered to reflect severe problems with physical functioning" (European Journal of Public Health 2009;20:3:251-257).

Common sense would suggest that a mathematically-derived recovery threshold which allows a participant to deteriorate and still be described as recovered must contain a mistake. Yet common sense has not prevailed in this instance and the co-editor-in-chief of Psychological Medicine (Professor Sir Robin Murray, Professor of Psychiatric Research at The Institute of Psychiatry; Fellow of the Royal College of Psychiatrists; elected a Fellow of the Royal Society in 2010 and knighted in 2011 for his services to medicine), has declined to correct obvious errors when they were pointed out to him.

No reduction in State or insurance benefits claimed

The Investigators and the DWP anticipated that there would be a reduction in participants' benefit uptake at the conclusion of the PACE trial on the basis that participants claiming such benefits would be able to return to gainful employment, whereas in fact there was an increase in benefit uptake from baseline to follow-up (Adaptive Pacing,

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Cognitive Behaviour Therapy, Graded Exercise, and Specialist Medical Care for Chronic Fatigue Syndrome: A Cost-Effectiveness Analysis. McCrone P et al. PLoS ONE Aug 2012;7(8):e40808, hence the DWP got no return on its investment in the PACE trial.

Client Service Receipt Inventory and the Investigators' refusal to release data owned by tax payers (who funded the PACE trial)

A basic tenet of scientific research is that data generated in a clinical trial is made available to other scientists for the ultimate benefit of sick people.

Currently there is a campaign being run by Dr Ben Goldacre of "Bad Science" and the major UK medical journals calling for all data from all clinical trials to be made public, with participating journals saying they will not publish the results unless all data, suitably anonymised, are made available.

Even though they do not own the data – since the PACE trial was funded by UK taxpayers -- the Investigators have persistently refused to comply with this requirement, which is why interested parties have made numerous FOIA requests.

The Protocol stated: *"The Client Service Receipt Inventory (CSRI), adapted for use in CFS/ME, will measure hours of employment/study, wages and benefits received, allowing another more objective measure of function"*.

The Investigators collected the data but have not delivered what was required in that they have not published the number of participants who were able to return to gainful employment or education at the conclusion of the PACE trial. Despite numerous requests for the number of participants who were able to return to (or be available for) full-time employment, the Investigators repeatedly refuse to supply these important figures.

The figures may never be obtained, since in a FOIA request for withheld PACE trial data, the Judge in the UK Information Rights Tribunal Appeal Judgment on Appeal No: EA/2013/0019 handed down on 22nd August 2013 ruled that *"academic freedom"* takes precedence over individual (or public) interest.

The Investigators justified their failure to provide the return to employment figures thus: *"Return to work is not, however, an appropriate measure of recovery if the participant was not working before their illness"* (Recovery from chronic fatigue syndrome after treatments given in the PACE trial. PD White et al. Psychological Medicine 2013; Oct; 43(10):2227-35 Epub ahead of print).

This raises the issue of why the Investigators included it as a measurement of successful outcome in their original protocol.

When it was pointed out by the Medical Advisor to the ME Association in a letter to Psychological Medicine that such figures would have constituted a useful measurement of recovery, Professor Peter White attempted to defend this failure: *"follow-up at six months after the end of therapy may be too short a period to affect either benefits or employment. We therefore disagree with Shepherd that such outcomes constitute a useful component of recovery in the PACE trial"* (<http://www.meassociation.org.uk/2013/07/pace-trial-letters-and-reply-journal-of-psychological-medicine-august-2013/>).

The Clinical Global Impression (CGI)

Out of the reports submitted on the participant-rated CGI (clinical global impression) of change in overall health at the end of the trial, 60% of participants in the GET group and 58% of participants in the CBT group reported negative or minimal change.

The Investigators were not, after all, studying ME/CFS

The PACE trial Patient Clinic Leaflet that encouraged patients to become participants stated: *"Chronic fatigue syndrome" is "also known as post-viral fatigue syndrome, myalgic encephalomyelitis (ME) or myalgic encephalopathy (ME)"*, thus there can be no doubt that patients with the neuroimmune disease ME were alleged to have been included in the PACE trial.

Not only did the Investigators remove the requirement for the pathognomonic feature of ME from their own (diluted) version of the "London criteria" (so that it was effectively the same as their own Oxford criteria), but because of significant problems with recruitment, on 14th July 2006 Professor Peter White sought approval from the West Midlands Multicentre Ethics Committee to advertise his PACE trial to doctors, asking them to refer anyone *"whose main complaint is fatigue (or a synonym)"* to enter the trial.

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ME/CFS is a classified nosological entity in the WHO International Classification of Diseases in which the pathognomonic feature is post-exertional fatigability; this is very different from “fatigue”, so just how scientifically rigorous the inclusion of patients with “*fatigue (or a synonym)*” in a clinical trial that claimed to be studying ME/CFS might be has not been addressed by the Investigators.

The Investigators focused only on “fatigue” and ignored other significant and well-documented signs and symptoms associated with cardiovascular, respiratory, neurological, endocrinological, immunological, gastro-intestinal and musculo-skeletal system dysfunction; in particular, the Investigators disregarded the robust literature on vascular and inflammatory problems in ME and the documented increased risk of cardiovascular events in relation to exercise in patients with ME.

Ethical approval and funding were granted on the basis that the Investigators would be studying “CFS/ME”, but after the trial ended and selected results had been published in The Lancet, in March 2011 Professor Peter White wrote to the editor of The Lancet saying: “*The PACE trial paper...does not purport to be studying CFS/ME but CFS defined simply as a principal complaint of fatigue*”.

A “*principal complaint of fatigue*” is not ME/CFS (a classified neurological disorder in ICD-10 at G93.3), yet the Investigators stated in The Lancet: “*The PACE findings can be generalised to patients who also meet alternative diagnostic criteria for chronic fatigue syndrome and myalgic encephalomyelitis*” (The Lancet: February 18, 2011: DOI:10.1016/S0140-6736(11)60096-2).

To regard and manage them – whatever definition used -- as a single behavioural disorder is a cause for concern because interventions that may be suitable for those with chronic “fatigue” may be harmful and even fatal for someone with ME/CFS.

Professor White’s belief about ME/CFS

Professor White’s belief about ME/CFS is contained in his contribution to the standard medical textbook (Clinical Medicine, edited by Kumar and Clark) in which ME/CFS is listed under “Functional or Psychosomatic Disorders: Medically Unexplained Symptoms”, which Professor White states were previously known as “*all in the mind’; imaginary and malingering*”.

In June 2004 Professor White was awarded an OBE for his work on “CFS”. The citation was: “*For services to medical education*”. Notices circulating at the time proclaimed him as leading the research into CFS/ME and said his OBE was a “*well-deserved honour and acknowledgement of his contribution to work on CFS/ME*”.

For someone to receive such an honour seems surprising if the person so honoured is apparently ignorant of the established facts pertaining to the subject of his research interest for which he was honoured.

Almost a decade later, despite the emerging biomedical science that further disproves his beliefs about the non-organic basis of ME/CFS, his beliefs remain entrenched and have not changed with the advancement of medical science.

The peer-reviewed research data do not support his beliefs that ME/CFS is a functional somatic syndrome; on the contrary they disprove his beliefs because there is clear and convincing evidence of organic abnormalities in ME/CFS, including evidence of:

disrupted biology at cell membrane level; **abnormal brain metabolism**; widespread cerebral hypoperfusion; **central nervous system inflammation and demyelination**; hypomyelination; a **complex, serious multi-system autoimmune disorder**; significant neutrophil apoptosis; a **chronically activated immune system** (eg. the CD4:CD8 ratio may be grossly elevated); diminished NK cell activity; **abnormal vascular biology, with disrupted endothelial function**; **significantly elevated levels of isoprostanes**; **cardiac insufficiency -- patients are in a form of cardiac failure**; autonomic dysfunction (thermodyregulation; frequency of micturition with nocturia; labile blood pressure; pooling of blood in the lower limbs; reduced blood volume with orthostatic tachycardia and orthostatic hypotension); **respiratory dysfunction, with reduced lung function in all parameters tested**; neuroendocrine dysfunction (notably HPA axis dysfunction); **recovery rates for oxygen saturation that are 60% lower than those in normal controls**; **delayed recovery of muscles after exercise** (note: there is no evidence of deconditioning); **evidence of a sensitive marker of muscle inflammation**; reduced size of the adrenal glands by 50%, with **reduced cortisol levels**; evidence that up to 92% of ME/CFS patients also have irritable bowel syndrome (IBS); **at least 35 abnormal genes (acquired, not hereditary), specifically those that are important in energy metabolism**; **there are more abnormal genes in ME/CFS than there are in cancer**; **serious cognitive impairment (worse than occurs in AIDS dementia)**; **adverse reactions to medicinal drugs, especially those acting on the CNS**; symptoms fluctuating from day to day and even from hour to hour. There is no evidence that ME/CFS is a psychiatric or behavioural disorder.

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For individual references, see: (i) www.meactionuk.org.uk/Organic_evidence_for_Gibson.htm and (ii) www.meactionuk.org.uk/What_the_Experts_say_about_ME.htm).

Many people around the world (ie. not just in the UK) believe that there is a pressing need for the removal of those currently in charge of the ME/CFS programme in the UK because, as Professor Stephen Holgate, MRC Clinical Professor of Immunopharmacology and Honorary Consultant Physician at the University of Southampton said at the CFS/ME Workshop held on 19th/20th November 2009 at Heythrop Park, Banbury, near Oxford: **it is time to get away from old models and to use proper science.**

On 2nd July 2013 Professor Holgate addressed the Forward ME Group in the House of Lords; **he called for radical change in ME/CFS research and said some researchers new to the field had been shocked by the poor quality of much ME/CFS research; he commented that some individuals had “made a career” out of ME/CFS theories that could be shaky and it was clear that this had to change** (<http://www.meassociation.org.uk/?p=16383>).

Such change has not yet happened and Professor White’s influence remains intact: in the UK Information Rights Tribunal Appeal Judgment on Appeal No: EA/2013/0019 handed down on 22nd August 2013 in which the Appellant sought information on the PACE trial under the FOIA, the Judge stated that Professor White “*listed the considerable commitment he had to make on a continual basis to defend and justify his work*” and quoted Professor White’s evidence: “*I have had to provide responses to Parliamentary Questions from members of both Houses of Parliament to allow them to understand the nature and findings of the PACE trial. In particular, I had to recently brief several members of the House of Lords so that they might speak in a critical debate about the PACE trial held on 6th February this year*”.

This explains why the House of Lords “debate” on 6th February 2013 was not a debate at all on the issues raised by the Countess of Mar but merely a platform for undiluted praise of the PACE trial and why the Medical Advisor to the ME Association had cause to write on 8th February 2013 on an internet forum: “*I was at the House of Lords ...for the debate. Sadly, I thought it was a very disappointing debate because after the Countess of Mar had made her speech, everyone else basically just read out prepared speeches with gave uncritical support to all aspects of the PACE trial*”.

What remains unaddressed by Professor White and his colleagues who favour the “behavioural model” of ME/CFS is why there have been so many questions raising concerns about his work on ME/CFS in both Houses of Parliament and why he has had to “*defend and justify his work*” on “*a continual basis*”.

Given that for nine months between February and October 2010 Professor White was granted leave of absence while he completed the PACE trial (necessitating the employment of locum Consultant cover for him at Barts), such leave of absence may have afforded Professor White enough time to address the legitimate issues raised with the transparency and speed required by his funding bodies.

In its Terms and Conditions relating to its grants, MRC-funded authors have a responsibility to report accurately and without obfuscation, and the MRC requires grant-holders to adhere to its policy on data-sharing which is built on the OECD report “Promoting Access to Public Research Data for Scientific, Economic and Social Development”. That report identified that publicly-funded research data are “*a public good, produced in the public interest and should be openly available to the maximum extent possible*”. The MRC specifically states that it expects “*valuable data arising from MRC-funded research to be made available to the scientific community with as few restrictions as possible so as to maximise the value of the data for research and for eventual patient and public benefit*” and that such data “*must be shared in a timely and responsible manner*”. It also states: “*Our data-sharing policy applies to all MRC-funded research*”; and it requires that results from this data-sharing “*should meet the high standards of all MRC research regarding scientific quality, ethical requirements and value for money*”.

Clearly, special pleading must relate to the PACE trial, as those Terms and Conditions have not been met by the PACE trial Investigators, yet they have not been subjected to any admonishment for their failure to comply with the MRC’s own stipulations.

For the last 25 years, Professors White, Sharpe, Chalder and Wessely have insisted that ME is not an organic disease and their extensive published outcome provides evidence of their beliefs.

Those beliefs are at variance not only with the substantial biomedical evidence-base on ME/CFS that has emerged since the 1980s but also with the evidence of the world’s premier virologist, Dr Ian Lipkin, Professor of Neurology and Pathology and Director of the Centre for Infection and Immunity at Columbia University, who has recently publicised his current work on ME/CFS: “*Many of these patients had evidence of immunity inflammation....the primary cause which I still believe is likely to be an infectious agent*”.

Professor Lipkin referred to the dismissal of ME/CFS as a psychological illness and to his own work on ME/CFS in 1997: “*As many of you will recall, there was a very strong sentiment in some portions of the scientific community, not all of it,*

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that this is a psychological illness....Based on our findings, we had very strong evidence that people with Chronic Fatigue Syndrome are ill. It was a real, physical illness and they deserved a deep dive to find out why they were ill".

He concluded: *"Our evidence suggests, based on the cytokines...that there is, in fact, ongoing stimulus to the immune system which results in activation and may well account for many of the symptoms associated with the disease"* (CDC PCOCA Conference Call, 9th September 2013).

Two years previously, reporting in November 2011 on their work on ME/CFS using multiple deep sequencing platforms, Professors Ian Lipkin and Mady Hornig were clear: Professor Hornig said they had good reason to believe there was an infectious trigger and both Professors Lipkin and Hornig stated that they do not consider ME/CFS to be psychosomatic: Professor Hornig said: *"It's very difficult in my mind to make this a psychological disorder....that shouldn't ever be viewed as being the primary problem"* (Cure Talk; ME Association website, 4th November 2011).

It is worth reiterating that it was thirteen years ago that Professor Anthony Komaroff, Professor of Medicine at Harvard, said: ***"There is now considerable evidence of an underlying biological process which is inconsistent with the hypothesis that (ME/CFS) involves symptoms that are only imagined or amplified because of underlying psychiatric distress. It is time to put that hypothesis to rest"*** (Am J Med 2000:108:99-105).

Even fellow psychiatrists now point out: *"a purely cognitive-behavioural model of CFS seems less explanatory for the pathophysiological disturbances identified so far...Nonetheless, the (behavioural) model is the main rationale of cognitive-behavioural therapy (CBT) and graded exercise training (GET) which are currently both recommended as first-line treatments"* (Boudewijn Van Houdenhove et al; Fatigue: Biomedicine, Health & Behaviour: doi:10.1080/21641846.2013.795085).

The PACE Investigators and those who share their beliefs about ME/CFS are clearly wrong in their assertion that ME/CFS is a psychological disorder and the very poor results of the PACE trial serve to substantiate how wrong they are.

In summary:

Despite the enormity of the media/medical spin on "recovery" surrounding it, the duplicitous utterances and excuses, and all the re-calculations of the data, the PACE trial failed.

It was wrong to focus on the small number of participants who, it is alleged, made a moderate improvement (which the Investigators themselves admit may not be maintained over time) whilst totally ignoring the vast majority (roughly two thirds) who were not helped by the interventions.

The PACE trial protocol claimed: *"The main aim of this trial is to provide high quality evidence to inform choices made by patients, patient organisations, health services and health professionals about the relative benefits, cost-effectiveness, and cost-utility...of the most widely advocated treatments for CFS/ME"*.

It was one of the PACE Principal Investigators themselves, Professor Michael Sharpe, who went on record about the results of the PACE trial; on 18th April 2011 he said on Australian radio: *"What this trial isn't able to answer is how much better are these treatments than really not having very much treatment at all"*.

The Science Media Centre's misrepresentation of the PACE trial results to the media

The emanations from the Science Media Centre (SMC) may be accepted by informed observers to be suspect because it represents only one narrow section of the scientific community (<http://ngin.tripod.com/020602c.htm>) but its wildly exaggerated press briefing for the PACE trial on 17th February 2011 was a travesty *par excellence*.

The SMC produced and publicised the opinions of clinicians known for their adherence to the behavioural model, including some physicians – such as Dr Alastair Miller and Dr Brian John Angus – who were involved in the PACE trial itself. For example, the Science Media Centre Press Release included the following:

- Dr Alastair Miller from Liverpool: ***"This trial represents the highest grade of clinical evidence – a large randomised clinical trial, carefully designed, rigorously conducted and scrupulously analysed and reported. It provides convincing evidence that GET and CBT are safe and effective and should be widely available for our patients with CFS/ME"***.

It should be noted that Dr Miller was one of the three "independent" assessors of trial safety data for the PACE

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Trial.

As the PACE Trial was not a controlled trial, Dr Miller was in error to refer to it as: **“the highest grade of clinical evidence”**, and it cannot be described in such terms.

- Dr Brian John Angus: **“The study should reassure patients that there is an evidence based treatment that can help them to get better.... It was extremely rigorous... (and) was carefully conducted....As a trial this involved a huge amount of checking and cross checking....This should mean that GET and CBT should be widely available throughout the country....The trial was conducted to a high ethical standard... .It was rigorously performed”**.

Dr Angus was Centre Lead for the PACE Trial in Oxford.

- Professor Derick Wade from Oxford: **“The trial design of this study was very good, and means the conclusions drawn can be drawn with confidence. This is a very significant finding. It identifies that one commonly used intervention (by which he meant pacing) is not effective (and therefore should not be used), and it confirms the effectiveness of two treatments, and their safety. The study suggests that everyone with the condition should be offered the treatment, and every patient who wishes to be helped should be willing to try one or both of the treatments”**.

The implication of this is that if people refuse to take part in these “rehabilitation” programmes, they do not wish to get better, so they can expect their State benefits to be withdrawn. Professor Wade has notably written to the DWP advising that, despite the WHO classification, ME/CFS is not a neurological disorder but a **“non-medical illness”** (letter dated 22nd August 2005 to Dr Roger Thomas, Senior Medical Policy Advisor in the Benefit Strategy Directorate at the DWP). He has also written to an ME/CFS patient: **“it is wrong to fit ME/CFS into a biomedical model of illness”** (letter dated 7th July 2006).

- Dr (now Professor) Willie Hamilton: **“This study matters. It matters a lot....It sends a powerful message to PCTs – and the soon-to-be-formed GP consortia – that they must fund CBT or GET. NICE proposed this before the study came out – the evidence is stronger now”**.

Dr Hamilton is Chief Medical Officer for three permanent health insurance companies -- Exeter Friendly Society, Liverpool Victoria and Friends Provident – and he categorises ME/CFS as a functional disorder. (People diagnosed as having this disorder will thus be excluded from payments under a permanent health insurance policy with these companies, since psychiatric disorders are not covered). He was a member of the NICE CG53 Guideline Development Group which recommended CBT/GET as the only intervention for people with ME/CFS.

(On 25th September 2013 NICE confirmed that they will not be reviewing their 2007 Guideline on CFS and that it is to be placed on their “static” list of guidelines that require only occasional revisiting instead up regular up-dating).

The Science Media Centre has been absolutely fundamental in misrepresenting and acclaiming the results of the PACE trial to the media. At the PACE trial press briefing, a number of grossly inflated and quite unjustified claims were made that are not supported by evidence and the Science Media Centre supplied and publicised quotations only from people with known and indisputable biases and with vested interests in maintaining the misperception of ME/CFS as a functional (behavioural) disorder.

The SMC’s press briefing did not address how it is acceptable for a trial to be hailed as the “gold standard” when, even after numerous deviations from the protocol and many re-calculations of thresholds, it resulted only in moderate benefit to around 10% - 15% of participants over and above the benefit of standard medical care.

In fact, 70% - 72% of all participants were not in the Investigators’ chosen (unduly low) “normal range” for fatigue and physical functioning at the end of the trial. The participants’ own views of their improvement were much less positive than the spin given in the SMC press briefing – roughly two thirds said that they had little or no improvement in their overall health but this was not reported in the media.

Consideration of the PACE trial data dispels the assertions quoted above so it was essential for the protection of vulnerable patients that a more balanced interpretation of the PACE trial findings was supplied to the media and thus entered the public domain, but the Science Media Centre did not ensure any such dissemination.

Following publication of selective results of the PACE trial in The Lancet, Swiss Re’s UK Life & Health Claims team arranged a web-based training session with Professor Peter White; it was called “Managing claims for fatigue the active way” and it was explicit: **“It will likely take time before the general public and some medical professionals accept the findings of this research....Key takeaways for claims management....It is likely that input will be required to change a claimant’s beliefs about his or her condition and the effectiveness of active rehabilitation”**, hence the PACE trial Investigators’ deceptions

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about ME/CFS are not merely an academic matter: they have led to vile sentiments such as these, where it becomes acceptable practice for insurers to coerce sick people into believing things that are demonstrably untrue.

Another key takeaway for claims managers said: *“A final point specific to claims assessors, and a question we’re often asked, is whether CFS would fall within a mental health exclusion, if one applies to the policy. The answer to this lies within the precise exclusion wording. If the policy refers to functional somatic syndromes in addition to mental health, then CFS may fall within the exclusion....The point made is that a diagnosis of ME is considered a neurological condition according to the arrangement of the ICD...whereas CFS can alternatively be defined as neurasthenia which is in the mental health chapter of ICD-10”.*

These psychiatrists who work for the insurance industry have been notified more than once that their assertion that ME/CFS has dual classification in the WHO International Classification of Diseases (once in the Neurological Section at G93.3 and also in the Mental (Behavioural) Section at F48.0) is incorrect. Their false assertions have been repudiated by the WHO, who on 23rd January 2004 confirmed in writing: **“According to the taxonomic principles governing ICD-10, it is not permitted for the same condition to be classified to more than one rubric”.** The WHO further confirmed that this means that ME/CFS **cannot** be known as or included with neurasthenia or any other mental or behavioural disorder, as ME/CFS is a distinct nosological disorder.

The readily-provable facts are that the PACE Investigators who work for the insurance industry pay no heed to the WHO classification, to scientific exactitude, to an international biomedical evidence-base on ME/CFS, nor to patients with ME/CFS because, it appears, profits must take precedence over patients.

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September 24th 2014

Agency for Healthcare Research and Quality
Office of Communications and Knowledge Transfer 540 Gaither Road, Suite 2000
Rockville, MD 20850.

Dear Sir/Madam,

I am an American citizen temporarily living in Ireland. I am contacting you in relation to your web page <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1906>

which contains several serious errors and omissions. I have detailed them below

- ME/CFS is not a "constellation of symptoms, with post-exertional malaise and/or chronic and disabling fatigue being the hallmark."
It is a physical biological illness, classified by the WHO as neurological, originating from a viral or other pathogen infection(s) and accompanying immune dysfunctions and subsequent neurological, endocrine, mitochondria and cardiac abnormalities, or in some cases organophosphate or toxin poisoning which causes some of the aforementioned abnormalities. The post-exertional malaise and disabling fatigue is a consequence of this, in a similar way to that encountered in Cancer, cardiac illnesses, diabetes, MS and other neurological illnesses.
- The "term ME was first used in the 1930s after an outbreak of neuromyesthenia" is a lie and factually wrong. ME was first used to define the illness by Dr. Donald Acheson in the Lancet medical journal in 1955 and has been used ever since - Outbreak at the Royal Free. E.D. Acheson. The Lancet, Volume 266, Issue 6886, Pages 394-395, 20 August 1955.
- "CFS was first coined in the 1980s".

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The term 'CFS' was used to describe an ME outbreak in Lake Tahoe in the mid 1980's. The very term 'CFS' is misleading and unscientific, and this was deliberately done by a Dr. Straus who wished

to make ME disappear by using a new invented term 'CFS'. This term was then perverted into an unspecific psychological illness by certain individuals in the CDC and NIH. Dr. Straus' letter to Dr. Fukuda shows an attempt to do this, and leave many patients with no proper diagnostics and no proper treatments for a serious biological illness <http://www.me-ireland.com/straus/straus.htm>
This has had serious consequences, including premature death for many patients - <http://www.ncf-net.org/memorial.htm>

ME is ME, it should not have been called 'CFS' or any other name. So let us call ME what it really is 'ME' and diagnose and treat it as a biological illness.

- "Over the years, there has been disagreement on the underlying etiology and whether the conditions represented by these terms reflect a single pathologically discrete syndrome, subsets of the same illness, or a nonspecific condition shared by other disease entities"

This is factually wrong. ME has been well documented since 1955, the WHO classified it in 1969.

Please read www.me-ireland.com and learn the facts about ME and outbreaks and epidemics prior to and after 1955.

- "The first set of clinical criteria defining the condition were published in 1988"

This is factually wrong. The first clinical criteria were described and used by Dr. Acheson in 1959, updated by Dr. Richardson in the early 1960's and by Dr. Ramsey in 1986

Dr. Acheson

[http://www.me-](http://www.me-ireland.com/Acheson1959.pdf)

[ireland.com/Acheson1959.pdf](http://www.me-ireland.com/Acheson1959.pdf) Dr.

Richardson

<http://www.cfstreatmentguide.com/blog/category/whos%20who%20in%20the%20cfsme%20communitya97fd2fd3b>

Dr. Ramsey

<http://www.cfids-me.org/ramsay86.html>

- "The variable symptomatology and lack of an identifiable disease process with gold standard of measurement have challenged researchers and clinicians in their attempts to better understand the disease process and its effects on patients."

This is the direct result of calling ME and CFS psychological illnesses. Most doctors and researchers have been told these lies for over 25 years, and this belittling and mocking of the illness as psychological and "all in the mind" has resulted in very little or no government, academic and private funding for research into ME. The illness ME has been starved of research for 25 years. The NICE clinics in Britain forbid many biological tests to identify subgroup biomarkers for the illness.

Patients and patient groups with their own personal funds have funded some biological research into ME, and a few governments have put a small amount of funding into biological research over

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the years. From this have emerged some biological biomarkers for subgroups. A few biological biomarkers have been found for the illness, please view www.me-ireland.com/scientific.htm

- "Thus finding ways to accurately diagnose patients to optimize management has significant public health importance and consequences."

Start doing biological tests and stop using the subjective and useless psychological tests. Then you will make some progress in the area of diagnostics and treatments. You could start here at <http://www.me-ireland.com/structure.htm#8>

- "Currently there are no U.S. Food and Drug Administration (FDA) approved medications for the treatment of ME/CFS"
The FDA can fast track psychological and psychiatric treatments, and regularly ignores dangerous side effects when approving these new drugs and treatments. It breaks its own rules. Using this logic, it should be able to fast track Ampligen and other biological treatments for the ME subgroups.
- The Fukuda criteria 1994 do not describe ME or CFS. The criteria is vague and ambiguous, it is unscientific, un-medical, and could be describing any number of illnesses, biological or psychological. It lacks specificity and sensitivity. It deliberately omits important medical and scientific findings in 1994 and prior to 1994. The criteria actually describes nothing and was open to abuse and was abused. The letter by Dr. Straus to Dr. Fukuda clarifies these points <http://www.me-ireland.com/straus/straus.htm>
The criteria led to premature patient deaths, see <http://www.ncf-net.org/memorial.htm>
The Fukuda criteria needs to be declared null and void by the US Government and its constituent agencies such as the DHHS, NIH, CDC and IOM.
- " The Key Questions
 - What methods are available to clinicians to diagnose ME/CFS and how do the use of these methods vary by patient subgroups?
 - What are widely accepted diagnostic methods and what conditions are required to be ruled out or excluded before assigning a diagnosis of ME/CFS?
 - What is the accuracy and concordance of diagnostic methods?
 - What harms are associated with diagnosing ME/CFS?
 - What are the (a) benefits and (b) harms of therapeutic interventions for patients with ME/CFS and how do they vary by patient subgroups?
 - What are the characteristics of responders and non-responders to interventions? "

The answer to the above is detailed on <http://www.me->

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irelandl.com/structure.htm#8 .These are based on medical and scientific facts dating back to 1955.

I hope this fully informs you about ME. I would refer you to the web site www.me-ireland.com in any way I can to bring about effective biological based diagnostics and treatments for all ME patients.

Best Regards

David Egan

Response to the AHRQ Draft Systematic Evidence Review
(IOM and P2P project)

Sunday, October 19, 2014
Scientific Resource Center
Portland VA Research Foundation
3170 SW U.S. Veterans Hospital Road
Mail code: R&D 71
Portland, Oregon 97239

RE: **Diagnosis and Treatment of Myalgic
Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)**

I am deeply saddened that after 20 or more years of constructive input from the ME/CFS community and the credentialed doctors who have participated in documenting and researching ME/CFS, the government organizations that are affiliated with the CFSAC team have virtually ignored all the information from the true experts. The true experts on ME/CFS are those of us who have been fighting for our lives, some of us have been in this Petri dish for nearly 30 years and those few doctors who recognize and believe our true condition. I have received the most help from doctors and practitioners who are willing to think holistically and/or were involved in research that veers off from the normal medical charter. We are a collection of educated professionals who got sick and are receiving very little constructive help from the medical community. Even worse, we are looked upon as faking it, perceived to have psychological imaginings, abused by the medical community at large and therefore our culture at large.

There has been little sense of humanity toward our plight. We have kicked against the traces jeopardizing our own health to get attention and respect. Gratefully, there have been a few medical professionals who have seen the lack of humanity and have stepped forward while the medical community at large still ignores their evidence. An international collaboration of medical experts, IACFSME, have presented the Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: A Primer for Clinical Practitioners which is widely accepted by the ME/CFS Community as accurate. The Canadian Criteria Consensus has also been acknowledged by our community as a valid representative document.

We have stated numerous times the dangers of GET, which is known within our community as extremely detrimental and has been known to cause death in patients and yet it is still recommended in the medical community and by the CDC. CBT as well can have damaging effects. And yet, the medical community trudges forward chests held high that "they" "know" what is best, even though they are perplexed.

Do any of you see the ignorance here? The lack of compassion? The inability to question the system that you work within? That maybe just maybe the medical establishment as a whole does not have all the answers. That maybe just maybe this is a CRACK in our medical system that needs to be explored. That maybe just maybe we need to have the

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vehicle to drive into this CRACK and explore without doctors having their livelihoods destroyed for being compassionate and for doing no harm. By applying therapies that are detrimental, you are doing harm; by doing nothing, you are doing harm; by following the only track that is guided by the AMA and pharmaceutical companies, you are doing harm; by ignoring the ME/CFS community and the seasoned scientists who have dedicated themselves through compassion to ME/CFS, you are doing harm.

As phenomenal as medical science has become, the miracles that trained physicians can perform, it clearly does not apply in our specific case.

I am in support of the response by Mary Dimmock, Claudia Goodell, Denise Lopez-Majano, Jennie Spotila and Erica Verillo that is posted on Occupy CFS; <http://www.occupycfs.com/2014/10/15/evidence-review-comments-preview/>

Elizabeth C. Potter

Double Major B.A in Mathematics and Secondary Education minor in Computer Sciences

Software Analyst until 1985

ME/CFS patient since 1985

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ME and Graded Exercise Therapy

Volume 3 Issue 3 of the journal [Biology](https://doi.org/10.3390/biology3030606) 10.3390/biology3030606 contains an article by David Maughan and Michael Toth entitled “Discerning Primary and Secondary Factors Responsible for Clinical Fatigue in Multisystem Diseases” published on September 22, 2014. These are researchers from the Department of Molecular Physiology and Biophysics from the University of Vermont, Burlington, VT. The article’s abstract states the following:

Abstract

Fatigue is a common symptom of numerous acute and chronic diseases, including myalgic encephalomyelitis/chronic fatigue syndrome, multiple sclerosis, heart failure, cancer, and many others. In these multi-system diseases the physiological determinants of enhanced fatigue encompass a combination of metabolic, neurological, and myofibrillar adaptations. Previous research studies have focused on adaptations specific to skeletal muscle and their role in fatigue. However, most have neglected the contribution of physical inactivity in assessing disease syndromes, which, through deconditioning, likely contributes to symptomatic fatigue. In this commentary, we briefly review disease-related muscle phenotypes in the context of whether they relate to the primary disease or whether they develop secondary to reduced physical activity. Knowledge of the etiology of the skeletal muscle adaptations in these conditions and their contribution to fatigue symptoms is important for understanding the utility of exercise rehabilitation as an intervention to alleviate the physiological precipitants of fatigue.

This brings to mind several points. IF myalgic encephalomyelitis (ME) is a subtype of Chronic Fatigue Syndrome (CFS), which I don’t believe it is, then so should be any and all acute and chronic diseases in which fatigue is a common symptom, such as cancer, multiple sclerosis, heart failure, obstructive pulmonary disease, lupus, AIDS and so on. I have never seen Cancer/CFS or MS/CFS. Neither have I ever seen CBT and GET touted as the main, central, effective treatment for any of these diseases, except for the disease ME. I don’t think cancer patients, their families, and the general public would tolerate the only treatment options available to them being CBT and GET, no matter how cost effective that might be, in spite of the fact that it certainly would not be very therapeutically effective. No, the government has put billions of dollars into researching these diseases so that at this point in time they have treatment options available to them. Unfortunately, that is not the case with ME, which, throughout its history, has received a mere pittance in research dollars. Consequently, there are no treatment options available for ME. This makes this P2P study rather lame. This insufficiency and lameness is what the P2P report should have pointed out. Instead it produced a report with many flaws:

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- 1) The failure to be clear and specific about what disease was being studied
- 2) The acceptance of 8 disparate ME or CFS definitions as equivalent in spite of dramatic differences in inclusion and exclusion criteria
- 3) The bad science reflected in citing Oxford's flaws and then using Oxford studies anyway
- 4) The well-known problems with the PACE trial, yet giving credence to its recommendations of CBT and GET anyway
- 5) The flawed process that used non-experts on such a controversial and conflicted area
- 6) Flawed search methods that focused on fatigue
- 7) Poorly designed and imprecise review questions
- 8) Misinterpretation of cited literature.

But let's get back to the above referenced article which can be found at

<http://www.mdpi.com/2079-7737/3/3/606/htm> and is well worth your read. In the section describing ME, the authors state:

We begin our discussion with a condition for which the hallmark-defining symptom is fatigue. Myalgic encephalomyelitis [6], often referred to as Chronic Fatigue Syndrome in the United States [7], is a devastating neuroimmune disease [8,9] displaying global disruption of the nervous, immune and endocrine systems [6]. Approximately 0.4%–1% of the adult US population has ME/CFS [10], although the percentage may be far higher considering the lack of wide-spread recognition of the disease in the general population and by the medical community. Symptoms include marked physical and cognitive fatigue, unrefreshing sleep, and a prolonged recovery period in response to even modest physical or mental activity. Muscle pain and fatigue are common symptoms, even at rest. Patients often develop fibromyalgia, a related neuroimmune disorder distinguished by chronic widespread pain and allodynia (a heightened and painful response to pressure) [11].

Abnormalities are evident within the immune [12] and central nervous [13] systems that likely stem from defective oxidative and nitrosative pathways and a lower antioxidant status [14,15]. Mitochondrial function is depressed, with the severity of the disease correlating with lower oxidative phosphorylation, nucleotide transport, and ATP levels in blood neutrophils [16,17]. There is some evidence that compromised metabolic function extends to skeletal muscles [18] and other major organs [16]. In what may be a compensatory response, anaerobic metabolism is up-regulated via enhanced glycolysis [16,17]. The regulation may be structurally based in supramolecular complexes of glycolytic and glycogenolytic enzymes [19]. Cytoplasmic compartmentation and the formation of enzyme complexes probably boosts ATP production and, with further regulatory enhancement, may help alleviate the depressed aerobic metabolism evident in ME/CFS. However, any benefits of shifting from oxidative to glycolytic pathways may be offset, during periods of increased

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physical activity, by excess production of fatigue-producing metabolic by-products (phosphate and metabolic acids) [20].

Metabolic defects may also be reflected in abnormalities in blood flow regulation and mitochondrial function, some of which may be linked to altered endothelial nitric oxide (NO) [21] and hydrogen sulfide (H₂S) [22] metabolism. NO relaxes the smooth muscles that surround arterioles and arteries, increasing the flow of blood when required. In ME/CFS patients, reduced NO production by endothelial cells [21] may increase the constriction of arterioles and arteries, whereas a postulated deregulation of H₂S [22] may lead to an inhibition of cytochrome-c oxidase and thus a reduction in mitochondrial production of ATP. A reduced blood flow or mitochondrial ATP production in critical organs, including the skeletal muscles, brain, and brain stem, could elicit a variety of somatosensory symptoms of ME/CFS, including a diminished ability to perform physical activity. [23]

Skeletal muscle fatigue, the topic of interest here, likely contributes to post-exertional fatigue in ME/CFS. A small shift from fatigue-resistant, oxidative type I fibers towards oxidative, type II fibers occurs in some patients, with little or no attendant atrophy [24]. Nuclear magnetic resonance [25,26] and electromyography [27] reveal pathological features that are consistent with defective ion channel or receptor function [28,29,30]. Skeletal muscle mitochondrial function may also be blunted, as it is in blood neutrophils [16]. Oxidative stress [14,31] or autoantibodies [32] directed against mitochondrial proteins, plasma membrane proteins, or metabolic enzymes may play a role in the ME/CFS pathophysiology—all of which would lead to diminished physical activity. In addition, oxygen delivery to the patient's skeletal muscles is impaired [33], contributing to the metabolic insufficiency observed in the musculature of ME/CFS patients [34]

In evaluating ME/CFS-related muscle fatigue, it is unclear to what extent aging and deconditioning contributes to the disease phenotype. Incorporation of these variables (particularly the former) into reported studies has generally been ignored. Research focusing on this issue is sparse, although one recent report shows diminished function of ventilatory muscles during exercise in ME/CFS patients that appears to be attributable to deconditioning [35].

The above is certainly NOT medically unexplained fatigue, and as such ME should be removed from the CFS label by the very definition of CFS.

A very important point is found at the end of the article:

[Figure 1](#) summarizes the challenge that researchers face in discerning the extent to which disease-related muscle phenotypes related to the primary disease *versus* muscle disuse—

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and the extent to which rehabilitation exercise therapy may correct or reverse the progressive development of muscle fatigue. The hypothetical time lines depict the primary effect of the disease itself (magenta hatched line) and the secondary effect of deconditioning (blue hatched line) on muscle physiological function, superimposed on the inevitable decline of function due to aging (green hatched line). The cumulative fatigue phenotype is the sum of all three. Exercise rehabilitation, which essentially counteracts the muscle disuse/deconditioning that accompanies many diseases, may be able to effectively remediate that specific component of the cumulative fatigue phenotype (difference between blue and red line). While this general approach undoubtedly cannot alleviate all of the symptomology of the condition, it may provide some symptomatic relief and allow patients to retain a higher level of functionality.

An exception to the general utility of exercise rehabilitation is the one multi-system disease in which chronic fatigue is the hallmark symptom: ME/CFS. Even *graded* exercise therapy [99] is known to exacerbate ME/CFS by placing too much stress on the compromised systems, leading to a worsening of symptoms which may be injurious [100]. What is the recommended approach to easing muscle fatigue in ME/CFS? Proper nutrition combined with dietary supplements as needed, restorative sleep, and carefully pacing one's activities so as not to overtax the body [36].

One last point: the story often repeated by many ME patients is that they were very active before coming down with ME when their lives abruptly changed. Therefore, deconditioning cannot be the cause of their ME.

Sister Sandra Duma, OSF, MS Ed

Submitted October 8, 2014

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Comments regarding the AHRQ review for ME/CFS:

No specificity as to what illness is being studied - it appears many "Medically fatiguing illnesses" were lumped in the same category as ME/CFS.

ME/CFS is a complex, misunderstood illness. For the panel to be comprised of non-experts reviewing studies and making determinations regarding diagnosis and treatment that know nothing about ME/CFS is absolutely ridiculous.

Misinterpretation of cited literature. If the panel consists of persons with no prior knowledge of a complicated illness, and some literature reviews included persons with "fatigue" and not ME/CFS...plus have no understanding of the definitions used for inclusion and exclusion criteria, how can any recommendations be sound?

Recent biological findings published in the literature, including those demonstrating the harms done with exercise to ME/

CFS patients were not included. However, the Pace trial, with all its flaws and problems were included and obviously misinterpreted.

Medical Experts in ME/CFS have already adopted the Canadian Consensus Criteria for research and clinical purposes. This entire P2P workshop is a waste of time and tax payers dollars and should be cancelled.

Thank you for your attention to these critical concerns that affect all the patients debilitated by this illness, their families and health care providers.

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To: Scientific Resource Center, Portland VA Research Foundation

Re: AHRQ Draft Comparative Effectiveness Review: "Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome"

AHRQ has critically erred in assuming that CDC and other CFS case definitions have demonstrated sufficient sensitivity and specificity to capture the disease entity Myalgic Encephalomyelitis (ME), as well as similar entities observed in cluster outbreaks in the US in the 1980's which prompted CDC involvement and, ultimately, the creation of the CFS construct. Until this can be demonstrated, CFS definitions cannot be said to have been validated or necessarily relevant for those cases or, indeed, for any patients who meet extant criteria for ME, an entity that was clinically observed in epidemic and sporadic cases studied by Ramsay and others, recognized by WHO, and clinically defined years before the CDC's Holmes committee created the first CFS case definition. Further, as can be inferred from comparative analyses of their respective case definitions, and by the fact that there are patients who meet ME but not CFS criteria, ME cannot be classified as a subset of CFS.

AHRQ has failed to consider that CFS case definitions, and the patient groups they select, only overlap those of ME, rather than encompassing them. This is clearly illustrated by the fact that **there is no single necessary criterion shared both by extant ME and CFS case definitions except disease chronicity.** [1-5][†] Thus the AHRQ report's relegation of ME to a 'subset' of CFS has no sound logical or scientific foundation, and neither does its recommendation for a single all-encompassing ME/CFS definition.

AHRQ appears to have borrowed the combination term "ME/CFS" from NIH, which has quite recently begun using "ME/CFS" to mean the sum of any and all disease descriptions that include the terms CFS or ME, without any rationale for the inclusion of all such descriptions under a single clinical label, and lacking any formal or informal definition, let alone any kind of validation. The only truly formal use of the term "ME/CFS" was by the 2003 Canadian Consensus document [6], which sought to identify a legitimate clinical entity, as close as possible to previously described ME, from the excessively non-specific CFS constructs, while - perhaps unwisely - compromising on terminology. The term ME/CFS is also often used informally by clinicians, researchers, advocacy groups and patients for pragmatic purposes and to try to raise awareness of ME while acknowledging that ME is rarely given as a diagnosis in countries such as the United States, where most patients who better satisfy ME criteria have been diagnosed with CFS instead.

By adopting the flawed premise that a clinical entity that unifies all ME and CFS constructs can actually be said to exist, the NIH-tasked AHRQ report became a tautological exercise, incapable of doing what was most necessary: critiquing two decades of research based on diagnostic criteria that have insufficient specificity and thus offer little hope of elucidating the pathophysiology of, or identifying treatments for, the various conditions that are captured by broad case definitions. Instead, by adopting the premise that ME/CFS is a single entity that may be sufficiently described by any of the extant case definitions of CFS, NIH and AHRQ are only compounding the diagnostic problems in ME and CFS research, while obscuring the more distinct clinical entity known as ME - the only one with a definition drawn specifically from the clinical study of epidemic cases.

To quote Dr. A. Melvin Ramsay, author of that definition and a critic of the CFS construct:

"...the failure to agree on firm diagnostic criteria has distorted the data base for epidemiological and other research, thus denying recognition of the unique epidemiological pattern of myalgic encephalomyelitis." [1]

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In the interests of scientific rigor and proper disease surveillance, NIH/HHS must not conflate established case definitions that have not been demonstrated to describe the same clinical entity. The primary inadequacy of the AHRQ report is the *a priori* nosological and semantic error of conceptually subsuming ME within the CFS diagnostic construct without sufficient validation.

Absent a drastic revision of its current draft report that would reflect a real understanding of these fundamental nosological issues, I urge AHRQ to inform NIH that it cannot participate in P2P, nor publish an evidence review, on scientific and ethical grounds .

Kartik A. Parekh
Patient Advocate, NY

Submitted October 20, 2014

References and Note:

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- 4: Dowsett EG, Goudsmit E, Macintyre A, Shepherd CB. "Report from The National Task Force on Chronic Fatigue Syndrome (CFS), Post Viral Fatigue Syndrome (PVFS), Myalgic Encephalomyelitis (ME)." Westcare, 1994. pp. 96-98.
- 5: Goudsmit EM, Shepherd, C , Dancey P, and Howes S. "ME: Chronic fatigue syndrome or a Distinct Clinical Entity?", Health Psychology Update, 18 (2009), 26–31.
- 6: Carruthers BM, Jain AK et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. J Chronic Fatigue Syndr. 2003;11(1): 7-115.

† Excluding the Canadian Consensus definition of 'ME/CFS', which shares with CFS case definitions the symptom of generalized chronic fatigue as a necessary criterion.

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October 13, 2014

Re: Randomized clinical trial cited in your report:

Montoya JG., Kogelnik A.M., Bhangoo M., Lunn M.R., Flamand, L., Merrihew L.E., Watt T., Kubo, J.T., Paik J., Desai M. A randomized clinical trial to evaluate the efficacy and safety of valganciclovir in a subset of patients with chronic fatigue syndrome" Journal of Medical Virology. 2013; 85(12): 2101-2109.

This trial is mentioned in Table 2 (Trials of medications for ME/CFS) in row 5 for "Montoya et al. 2013"⁷¹

To Whom It May Concern:

Please correct following mistakes:

1. Our study design was randomized, double-blind, placebo controlled. This is one of the most robust designs in clinical trials and should be emphasized in your report.
2. For placebo we did not use "IV for placebo (1% albumen solution) every 30 days for 6 months (6 infusions)". That would have been clearly the wrong choice for a placebo in this study. We used a placebo-pill form that was identical to the valganciclovir pill. The information contained in your Table 2 under "Interventions" needs to be corrected.

You can see in the article, in the methods section (page 2102, last paragraph under "Study Protocol and Patients"): "Patients were given VGCV or placebo based on their assignment for 6 months and followed for 6 additional months. Patients and investigators were blinded for a total of 9 months from the start of randomization and until data were collected and locked onto three CDs. The packaging of VCGV and placebo was performed by Roche at their headquarters (Basel, Switzerland) and sent to the Stanford Pharmacy. VCGV or identical-appearing placebo was initiated at a dose of 900 mg (two 450 mg tablets) twice daily for 21 days followed by 900 mg once daily to complete 6 months"

3. You chose not to report other clinical endpoints that were statistically significant (but chose somewhat arbitrarily to include others that were not significant). Please add the following clinical endpoints that were statistically significant and support further the possibility of a clinical benefit in the treatment group when compared to the placebo group: MFI-20 mental fatigue subscore (P = 0.039); cognitive function (P = 0.025). You also chose to ignore that patients in the VGCV arm were 7.4 times more likely to be classified as responders (P = 0.029) before the blind codes were broken and made available to the investigators. From the article (Abstract section): "However, statistically significant differences in trajectories between groups were observed in MFI-20 mental fatigue subscore (P = 0.039), FSS score (P = 0.006), and cognitive function (P = 0.025). VGCV patients experienced these improvements within the first 3 months and maintained that benefit over the remaining 9 months. Patients in the VGCV arm were 7.4 times more likely to be classified as responders (P = 0.029)".
4. You also decided not to report key biological-immune endpoints such as the effect of valganciclovir effect on monocytes (an unknown biological effect of this drug until it was discovered in our study), neutrophils and cytokines. These should be added. From the abstract section of the article: "In the VGCV arm, monocyte counts

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decreased ($P < 0.001$), neutrophil counts increased ($P = 0.037$) and cytokines were more likely to evolve towards a Th1-profile ($P < 0.001$). And yes, contrary to our hypothesis and hope, we did not observe changes on the viral titers. It is important to include these biological effects since they support that CFS is a biological entity amenable to biological interventions.

5. Despite the fact that you judged this randomized clinical trial as “fair” in quality, you do not mention it in your “Structured Abstract” section: “Of the 36 trials on interventions, rintatolimod improved measures of exercise performance, compared with placebo; cognitive and behavioral therapy (CBT) and graded exercise treatment (GET) compared with no treatment, relaxation or support were found to improve fatigue, function, and quality of life, while CBT also improved employment outcomes. Other interventions either provided no benefit or evidence was insufficient to draw conclusions”.
6. On Table 2, this study is cited as reference 71 when it should be reference 60.

Please do not hesitate to contact me should you wish to discuss above comments or seek additional information. Transparency is the key to this process as long as there is an underlying good intention to bring scientific resources necessary to solve the ME/CFS puzzle.

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To: Scientific Resource Center Portland VA
Research Foundation

From: Michelle Strausbaugh

Re: Comments on AHRQ Draft Comparative Effectiveness Review on the Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Date: October 19, 2014

I wish to thank the members of Scientific Resource Center of the Portland VA Research Foundation for their careful efforts in wading through the complex body of research about ME/CFS at the request of the Agency for Healthcare Research and Quality to inform the Pathways to Prevention project on ME/CFS. I agreed with a number of findings in this draft report including

- suggestions with regard to future research priorities including the consistent use of a single case definition, studies seeking to distinguish ME/CFS from diseases that may present similarly (like depression, fibromyalgia, multiple sclerosis), larger trials with rigorous adherence to methodological standards, patient-centered outcomes in interventional studies such as quality of life, work and/or school attendance, and time spent supine, and designating PEM, neurocognitive status, and autonomic function as essential features to be studied in all future studies
- its attempt to examine the reporting -- or not reporting -- of harms across all treatment modalities as well as the harms associated with the diagnostic label of "chronic fatigue syndrome,"
- its conclusion that definitions of ME/CFS that require symptoms of Post- Exertional Malaise (PEM), neurological impairment, and autonomic dysfunction represent a group of patients with greater illness severity,
- its designating the Oxford definition as especially prone to including patients who may not have ME/CFS and would thus make study results unreliable and create even greater confusion in the evidence-base
- that lack of subgrouping of patients has been a significant barrier to understanding who will respond to treatments and has contributed significantly to diagnostic confusion
- that there is little to guide clinicians when there is diagnostic uncertainty
- that the quality of the evidence base is poor due to small sample sizes, lack of adequate blinding, and the wide variety of methods used to measure outcomes and randomize study participants (if randomization occurred at all)
- that, on the face of it, an examination of the evidence-base will suggest that CBT and GET show benefit in self-reported measures of fatigue, function,

and global improvement

Having said that, ***I have strong reservations about this draft report in its current form and endorse all concerns detailed in the Dimmock et. al. comments*** submitted to you on October 18, 2014, including:

- the focus on "persistent fatigue not attributable to a known underlying medical condition" and the *a priori* decision not to review treatment outcomes except for fatigue, making this an evidence review of medically- unexplained fatigue which may or may not include an evidence

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review of the disease(s) known as ME/CFS with its hallmark symptom of Post-Exertional Malaise (PEM) or Post-Exertional Neuro-immune Exhaustion (PENE)

- using all eight definitions interchangeably, despite evidence -- and even the Evidence Review's own concerns -- that these eight criteria do not necessarily represent the same group of patients all sharing the same underlying pathology; this was especially problematic with regard to the use of Oxford criteria in exercise and psychological therapies
- lumping all studies of Cognitive Behavioral Therapy (CBT) together without distinguishing between the two opposite primary treatment approaches to this intervention (or even explaining these approaches to the reader): the "false-illness beliefs" school of thought and the "energy-envelope" school of thought; the first seeks to challenge patients' beliefs about their illness with the intention that patients should *decrease their attention* to their symptoms, the latter seeks to teach patients to live within the limitations of their illness (the energy envelope) by *paying more attention* to their symptoms; moreover, this lumping of divergent forms of CBT also fails to acknowledge potential harms of CBT for a patient with an organic illness
- the failure to include a review of biomarker evidence including cardiopulmonary exercise testing and some clinical trials based on inappropriate duration criteria that could distinguish subgroups and/or diagnostic criteria as well as call into question the suitability of graded exercise therapy as a potential treatment intervention; Dimmock et. al's comment with regard to biomarker data is worth repeating here to underscore its importance: "Ultimately, patterns of common symptoms are not the solution to the diagnostic challenges of ME. Objective biomarkers are."
- a lack of discussion about the value of receiving a diagnosis of ME/CFS and the implication that receiving the diagnosis is harmful rather than the stigma surrounding the diagnosis in the medical community; moreover there is also a failure to adequately discuss the harms associated with being misdiagnosed with ME/CFS when patients have a different recognizable and treatable disease or with being diagnosed with a psychiatric disorder
- a failure to adequately review methodological flaws in the PACE trial which, due to its size, randomization, and comparative interventions design, resulted in the overstatement of the quality of evidence for CBT and GET; while the draft report does acknowledge it had no access to study protocols (though for the PACE trial they are readily available -- see White, et. al "Protocol for the PACE trial" BMC Neurol. 2007 Mar 8; 7:6) which would have allowed for a more thorough examination of outcome and analysis reporting bias, the draft report does not examine problems with the selection criteria, lack of actigraphy data, the anemic level of improvement across ALL interventions (even in the GET arm, patients remained very ill -- outcome measures like SF-36 scores and the 6min walk test demonstrate that ME/ CFS patients remained sicker compared to other diseases like pulmonary or congestive heart disease), post hoc changes to data analysis that theoretically could result in a patient entering the study functionally better than he/she ended it)
- several *a priori* decisions on treatment outcomes biased the analysis of treatment studies including the decision to focus on fatigue thereby excluding PEM, the almost exclusive use of self-report measures (which by their very nature are subjective), the lack of physical function outcomes, and the lack of objective outcomes such as actigraphy data; I cannot agree more with the Dimmock et al statement, "the *a priori* decision to focus on self-report measures and changes in fatigue (as opposed to other ME symptoms) narrowed the scope of the Evidence Review. Including studies that used changes in physiological measures like antibody titers would have broadened the number of interventions examined by the Review." This is particularly vexing given that treatments were examined with the expressed purpose of noting what they might reveal about etiology (while etiological studies were ignored), making it hard not to feel there is inherent bias in favor of behavioral studies

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- the failure to address how the paucity of funding for ME/CFS is a strong factor in why the evidence base is so small and of such poor quality; it is worth repeating Dimmock et. al.'s statement that "...niggardly research funding has restricted ME research to small pilot case-control studies, with a few larger studies looming over the landscape and potentially biasing this assessment of the field as a whole..."
- the failure to call for the use of objective data such as actigraphy in place of or in addition to self-reported measures
- as a result of the review protocol established by AHRQ, the draft report fails to address the broader but essential questions of whether ME and CFS are the same disease, if ME is a more severe subset of a larger CFS diagnostic

category, or if ME and CFS are separate diseases that should be studied separately; while the authors of the draft report are limited by this *a priori* assumption in the review protocol (which, in turn, dropped this question from the review protocol due to the lack of data available to answer such a question), this remains a fundamental ontological problem that absolutely must be addressed and should be at the very least explored in greater depth in this draft report regarding how the problem might be addressed by future research beyond a sentence acknowledging this issue as controversial

To Dimmock et. al.'s very thorough and careful analysis of the flaws of this draft report of the Evidence Review, I would add the following:

- with regard to potential methodological difficulties with the PACE trial, I would also note that there was concern expressed that the form of pacing used for the "adaptive pacing" intervention arm of the trial differs substantially from the type of pacing generally in use in the patient community(1) or that the "adaptive pacing" approach involved multiple forms of pacing (a term that itself is not well-defined within the medical community) that led to confusion about what kind of pacing was actually effective(2) (though it could be argued the PACE trial introduced a new combination version of pacing); the study authors stated that since there was no manual available for pacing, they created their own in collaboration with the patient organization Action for ME rather than create one based on what was being used in the research of Jason et al.(1999), Pesek et al. (2000), as well the popular online site CFIDS & Fibromyalgia Self-Help (www.cfidselfhelp.org) which has a self-help course that teaches pacing using the Energy Envelope theory and includes a textbook; given that the study authors were themselves involved in creating the "adaptive pacing" interventional arm despite materials available that were specifically based on the very Energy Envelope theory the PACE authors were ostensibly trying to test in their study, it is possible they may have consciously or unconsciously "underpowered" the comparative intervention
- there were nearly as many papers published on multiple sclerosis in the last year as indexed by PubMed (4529) as have been published on chronic fatigue syndrome since 1987 (5346); this is a shocking level of research neglect for a disease that, while it is true that MS has been a discreet medical entity since the late 19th century(3) and CFS has only been so since the mid-1980s, affects at least one million Americans, involves substantial morbidity and at potentially substantial cost to the US economy; while it is beyond the purview of the Evidence Review to examine and discuss federal funding policy of disease, it cannot be overstated how the paucity of funding for ME/CFS has impacted the current evidence base that has, in turn, created the current confusion about diagnosis and treatment of ME/CFS and I implore the study authors to include a discussion about how this dearth of funding has negatively impacted the evidence base.
- there has also been largely anecdotal concern expressed by advocates and ME/CFS researchers doing biomedical research that NIH has not taken ME/ CFS as seriously as would be expected for a disease with its prevalence and severity. The Special Emphasis Panel reviewing grant proposals

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for ME/ CFS research has been singled out at times for showing a sustained and significant bias in favor of behavioral studies (4), most likely due to a lack of knowledge of the disease (which the NIH vigorously denies saying the problem is that there are not enough proposals and/or that the proposals are not of an acceptable quality); any systematic evidence-based review would by its very nature eschew anecdotal reports, but it may be worth considering what potential forms of acceptable evidence there might be about potential bias in how public funds have been distributed in ME/CFS given the preponderance of behavioral studies

- while women are well -- if not overly -- represented in the studies included in this draft evidence review, given that ME/CFS is a disease of mostly non-specific symptoms, that it lacks basic clinically validated biomarkers, that it is more prevalent among women, and that women's health complaints have historically been discounted as "psychosomatic" or "hysteria" by traditionally male-dominated medicine(5), the preponderance of behavioral studies in the ME/CFS evidence base may represent a form of gender bias in which research favoring psychogenic etiology has been systematically favored over biomedical research

As the authors of this report and its future Pathways to Prevention panel-member readers well know, at the end of the day this systematic evidence review is not about science for science's sake. It is not a mere intellectual exercise. It is not simply an analysis of mythically value-free facts. It is about how to best inform the decision-making of a variety of "stakeholders" from policy making politicians and bureaucrats to health care providers all for the benefit of the patient. Many of these ME/CFS patients are providing comment on this draft evidence review because they are desperately ill, angry that so very, very, very little has been done to alleviate their suffering, and have almost all felt at one time or another that science and evidence based medicine are used in an authoritarian way to invalidate their experience of their illness. Please remember the variety of ways this evidence review will impact patients in very real ways -- both harmful and helpful.

1Charles Shepherd, "PACE trial: ME Association letter to 'The Lancet', 3 March 2011" ME Association website <http://www.meassociation.org.uk/2011/03/pace-trial-me-association-letter-to-the-lancet-3-march-2011/> (accessed Oct. 19, 2014)

2Johan WS Vlaeyen et. al "The PACE trial in chronic fatigue syndrome," The Lancet, Volume 377, Issue 9780, p1834, 28 May 2011 doi:10.1016/S0140-6736 (11)60682-X

3T. Jock Murray, Multiple Sclerosis: the History of a Disease (Demos: New York, 2005).

4 a few examples of this discussion can be seen at

"Chronic Fatigue Syndrome: CDC and NIH Research Activities Are Diverse, but Agency Coordination is Limited" GAO report to Senator Harry Reid June 2000

Craig Maupin "Scientific Review, CFS, and the NIH -- The CFS Special Emphasis Panel" at The CFS Report http://www.cfidsreport.com/Articles/NIH/NIH_CFS_3.htm

Cort Johnson "Unfulfilled Commitments/Broken Promises: The NIH and Chronic Fatigue Syndrome After Twenty-Five Years" at Health Rising <http://www.cortjohnson.org/blog/2013/12/22/unfulfilled-commitments-broken-promises-nih-chronic-fatigue-syndrome-twenty-five-years/>

Mindy Kitei "Candid Conversation with Dr. Ian Lipkin" at CFS Central <http://www.cfscentral.com/2014/05/candid-conversation-with-dr-ian-lipkin.html>
Lipkin, a renowned pathologist, is quoted as saying:

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"I have been in competition now twice to get funded, and the people there who reviewed me gave me abysmal scores. And the critiques of my work were unfair, and one of the people who critiqued my work said, in fact, that this is a psychosomatic illness. I was floored. I protested, and for reasons that are obscure to me this same individual wound up back on the study section, and I got a similar unfundable score. Am I upset about this? Absolutely."

5 Roberto Hernandez "Discrimination" in Sana Loue et. al. *Encyclopedia of Women's Health* (Kluwer Academic/Plenum Publishers: New York, 2004)
p.223

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10/18/14

Dear AHRQ:

I have been severely disabled by myalgic encephalomyelitis (ME) since 1994. I am largely bedbound, unable to shower, and can't walk more than a few steps. I require a nursing home level of care. I am unable to leave my home except for medical appointments once or twice a year.

Please answer the following questions:

- Why does your report never once mention the estimated 25% of ME patients who are homebound or bedbound, like me? Are you not aware of our existence, or did you deliberately choose to ignore us? If so, why?

The recommendations in your report are extremely harmful to people like me. As Dr. Ken Friedman said in a recent Medscape article, "If you're lying in bed and you can't move your head and you have to speak in whispers, graded exercise therapy is not going to help you, and were you to attempt it, it would most likely kill you."

- Why do you lump together eight case definitions? What proof do you have that they define the same clinical entity? Why do you ignore work that shows most of these definitions are unreliable and inaccurate?
- Why do you ignore critical cardiopulmonary and biomarker studies?
- Why do you ignore all symptoms except fatigue? I have such bad muscle weakness that I often cannot brush my teeth. Yet you ignore muscle weakness and other symptoms. Why?

Thank you. I support comments by Mary Dimmock, Claudia Goodell, Denise Lopez-Majano, and [redacted for patient privacy].

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To: Scientific Resource Center, Portland VA Research Foundation
Subject: Comments on AHRQ Draft Comparative Effectiveness Review: Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
Date: October 20, 2014

The AHRQ Evidence Review for “ME/CFS” has recommended CBT and GET, treatments that are based on the “fear avoidance” or biopsychosocial theory of CFS, a theory adopted particularly by those who use the Oxford definition and/or study the use of CBT and GET. This theory postulates that the disease is maintained by psychosocial factors, in particular maladaptive beliefs about being ill that has led to avoidance of activity and resultant deconditioning.^{xcii} Treatment with CBT and GET is intended to reverse illness beliefs, activity avoidance and deconditioning.

This biopsychosocial theory for CFS draws on the work of psychiatrist Dr. George Engel,^{xciii} who emphasized the importance of treating the whole patient and the need to avoid mind-body dualism by considering the role of the psychological and social factors in human disease.

But there is a vast difference between a humane understanding that heart disease might be aggravated by stress or lead to secondary depression and the idea that a contrived behavioral trait is the sole determinant that is keeping a patient sick. In the application of the biopsychosocial theory to CFS,^{xciii} the factors related to disease risk, causation and “maintenance” (persistence) are almost entirely devoid of biological pathology beyond acknowledging that an infection *might* have initially triggered the disease. Explanations for both the risk of developing the disease and for the persistence of the disease are almost exclusively grounded in psychological and behavioral problems and ignore the substantial evidence of underlying biological pathologies. In the guise of avoiding mind-body dualism, the approach has erased the body.

This focus on psychological and behavioral factors is so strong that it has resulted in CFS being dual listed as both a neurological disease and as a mental disorder in certain medical dictionaries and terminology systems, particularly in the U.K., in spite of the World Health Organization classifying CFS only as a neurological disease and explicitly ruling that CFS is not a mental illness.^{xciv} Further, a number of researchers have described CFS as the prime example of somatoform disorder/somatic symptom disorder, classified as a mental disorder in the DSM-5.^{xcv}

Many organic diseases like Alzheimer and cancer can be associated with psychological issues and/or reactive depression and yet, neither of those is listed in the mental health chapters of the above referenced dictionaries and terminology systems. As Dr. Richard Sykes states in a 2002 article,^{xcvi} the existence of a psychological issue is not sufficient reason to declare a disease to be a mental disorder. Sykes goes on to state, “There must be good grounds for thinking that particular psychological factors have a causal influence” and emphasizes, “The absence of a known physical cause is not grounds for imputing psychological causation.”

Citing the following factors, Sykes concludes that this disease has been inappropriately cast as a psychological illness:

- Psychological problems are not always present or when they are, are a consequence of the disease and not the predominant problem;
- The disease often starts with a flu-like illness from which patients do not recover; and
- There is substantial evidence of biological neurological and immunological abnormalities.

To Sykes point, no studies have demonstrated that psychological and behavioral issues are the driving factors behind the risk of getting this disease or its ongoing persistence. That is, unless one views as proof the results of studies done with Oxford, Fukuda and Reeves in which overly broad

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definitions and patient selection methods have selected patients with psychiatric disorders. But to do so is circular reasoning in which the presence of patients with psychiatric disorder can be expected to result in findings of significant psychiatric factors. Further, such findings are not proof that the disease described by the Canadian Consensus Criteria and ME International Consensus Criteria is driven by such psychological factors or will respond to psychological treatments.

This Evidence Review is recommending CBT, a treatment whose therapeutic intent is to reverse the maladaptive behavior and personality factors presumed to be driving this disease. Given the points made by Sykes and the fact that predominant psychological and behavioral factors have not been proven in patients that meet the Canadian Consensus Criteria or the ME International Consensus Criteria, it is unethical and scientifically invalid to recommend such treatments for CCC and ME-ICC patients.

This Evidence Review needs to reassess these treatment recommendations in light of the psychologicalization that has been driven by the biopsychosocial theory of CFS. Further, this Evidence Review needs to decide whether the disease being evaluated is predominantly an organic disease, albeit with reactive depression or similar psychological issues or whether it is predominantly a disease of maladaptive personality and behaviors. It is nonsensical to postulate a single clinical entity that is both at the same time.

¹ PACE trial - Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *The Lancet* - 5 March 2011 (Vol. 377, Issue 9768, Pages 823-836) [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(11\)60096-2/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext).

- *The PACE trial, done in patients that met the Oxford definition, tested cognitive behavioral therapy (CBT) and graded exercise therapy (GET) which were used “on the basis of the fear avoidance theory of chronic fatigue syndrome” that “assume that the syndrome is perpetuated by reversible physiological changes of deconditioning and avoidance of activity.”*
- *PACE trial CBT Manual - <http://www.pacetrials.org/docs/cbt-therapist-manual.pdf> Page 81 - “It is important to include the precipitating factors, e.g., illness, life-events, working excessively hard, perfectionist personality etc. It is also important to discuss the maintaining factors, e.g., erratic or reduced activities, disturbed sleep patterns, unhelpful illness beliefs and any other unhelpful cognitions etc.*

¹ Borrell-Carrió, F., Suchman, A., Epstein, R. The Biopsychosocial Model 25 Years Later: Principles, Practice, and Scientific Inquiry. *Ann Fam Med* 2004;2:576-582. DOI: 10.1370/afm.245.

¹ The following two articles discuss this theory. The work of Wessely is referred to as the biopsychosocial approach where the work of Vercoulen was described by Maes as a psychosocial approach.

- Harvey, S. Wessely, S. Chronic fatigue syndrome: identifying zebras amongst the horses *BMC Med.* 2009; 7: 58. Published online Oct 12, 2009. doi: 10.1186/1741-7015-7-58 PMID: PMC2766380. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2766380/>
- Vercoulen JH, Swanink CM, Galama JM, Fennis JF, Jongen PJ, Hommes OR, van der Meer JW, Bleijenberg G. The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: development of a model. *J Psychosom Res.* 1998;45:507–517. doi: 10.1016/S0022-3999(98)00023-3.

¹ Examples include the following:

- Certain English institutions and government agencies have incorrectly stated that the term “CFS” is classified not only as a neurological disorder but also as neurasthenia. In the 2001 British *WHO Guide to Mental Health in Primary Care*, adapted from the WHO’s guide to mental health in primary care, England placed CFS not only in the neurological chapter but also under neurasthenia in the mental and behavioral disorders chapter. In 2001 and again in 2004, WHO staff issued a ruling that the placement under neurasthenia was incorrect.
- Summary of statement by World Health Organization about the dual classification http://www.theoneclickgroup.co.uk/documents/ME-CFS_docs/WHO%20STATEMENT.doc “Andre L’Hours, the Technical Officer at the WHO headquarters in Geneva who is responsible for the ICD, confirmed that it was “unacceptable” if the same disorder had been included in two places in the ICD-10 and that the same disorder could not be differently categorised under the one WHO banner.”
- *WHO Guide to Mental Health In Primary Care* published by the WHO collaborating Center at Kings College. It is not clear exactly when this was first published but it is on the 2001 version of this page. <http://web.archive.org/web/20010709061548/http://cebmh.warne.ox.ac.uk/cebmh/whoguidemhpck/disorders/f48-0.html>

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- The *Read Codes*, used as standard terminology in clinical practice in England, classifies CFS (and ME which is listed as a synonym of CFS) as both a neurological disorder and as a form of neurasthenia listed under somatoform disorders in the mental health disorders section.¹
 - Read Codes <http://systems.hscic.gov.uk/data/uktc/readcodes>
 - Read Codes, Clinical Terms Version 3 (CTV3) can be seen here <http://bioportal.bioontology.org/ontologies/RCD?p=classes&conceptid=http%3A%2F%2Fpurl.bioontology.org%2Fontology%2FRCD%2FXa01F>
- The *SNOMED CT* clinical terminology system, important to the implementation of electronic health records, lists CFS as a multisystem disorder but also as a mental disorder. ME is listed as a synonym of CFS and thus similarly classified
 - <http://www.ihtsdo.org/snomed-ct/>
 - Multiple browsers are available, including: <http://bioportal.bioontology.org/ontologies/SNOMEDCT?p=classes&conceptid=http%3A%2F%2Fpurl.bioontology.org%2Fontology%2FSNOMEDCT%2F52702003>
- Training Module for Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME) - Guidelines for the Disability Analyst. Continuing Medical Education Programme Provided On Behalf Of The Department For Work And Pensions. MED/S2/CMEP~0017 Version 7 Final Module: 6. May 28, 2014. <http://www.actionforme.org.uk/Resources/Action%20for%20ME/dwp-training-doc-for-assessors-on-me.pdf>
 - In 2014, the U.K. Department of Work and Pensions issued a training module for “CFS/ME” disability assessment,¹ which also incorrectly states that the ICD-10 classifies the disease as both neurasthenia and a neurological disorder. But the manual goes further and explicitly links CFS/ME to the term “somatic symptom disorder” in the new version of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. The manual states that somatic symptom disorder is a newer term for somatoform disorder.
- Treatments for Fibromyalgia in Adult Subgroups. Agency for Healthcare Research and Quality. Draft July 23, 2014. Page 30 of file, page 4 of second section <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayProduct&productID=1944> The July 23, 2014 draft evidence review for
 - *Treatment for Fibromyalgia in Adult Subgroups*,¹ published by AHRQ, referred to CFS as a “functional somatic syndrome”, a term widely equated to the terms “somatoform illness” and “somatic symptom disorder.”

¹ Examples of CFS being referred to as Somatorm illness.

- Overview - [Slide presentation](#) [PDF format] **Somatoform disorders – functional somatic syndromes – Bodily distress syndrome**. Need for care and organisation of care in an international perspective – EACLPP Lecture, Prof. Per Fink, MD, Ph.D, Dr.Med.Sc. www.functionaldisorders.dk
- Michael B. First, M.D., DSM Somatic Presentations of Mental Disorders (September 6-8, 2006). American Psychiatric Association. <http://www.dsm5.org/Research/Pages/SomaticPresentationsofMentalDisorders%28September6-8,2006%29.aspx>

¹ Sykes, R. Physical or mental? A perspective on chronic fatigue syndrome. *Advances in Psychiatric Treatment* 2002, 8:351-358. DOI: 10.1192/apt.8.5.351

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Comments on Review Draft Report to AHRQ, Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, 2014

My comments on the Review concern mainly the role of exercise studies in 'ME/CFS' with special reference to the PACE trial which has been considered 'good quality' in your Review and has been influential.

It is disappointing that the CBT/GET studies emerge as dominant sources of evidence on the role of exercise in 'ME/CFS' in this Review. The authors conclude that CBT and GET 'show some benefit' but have only 'moderate confidence' in these benefits while noting that 'GET was associated with a higher number of reported harms and withdrawal rates in several trials'.¹ Indicators of these harms named in the Review are patient drop-outs, follow-up failures and poor physical performance the exercise studies.¹ These are found in the 6 Minute Walking Test (6MWT) in PACE (See below)² a step test³ and a treadmill test.⁴

The Review has not highlighted the fact that the conclusions of the CBT/GET studies mostly rely on outcome measures consisting of self-reported tick-a-box tests measuring a variety of dimensions. When these measures show improvement, however modest, the authors declare them a success without regard to the frequent failure of the treatments to translate into significant improvement in objectively measured physical performance, the result sought by patients. They persist with the treatment, without questioning their assumptions about the condition they purport to treat and ignore the biomedical evidence underlying the condition.

These unfavourable results should send the reviewers in search of possible explanations in the literature. Instead, we find that biomedical studies addressing these issues have been excluded because they failed to meet various formal inclusion criteria.¹

Examples of exclusion are the CPET studies which identify abnormalities in impaired heart rates and lower oxygen consumption on the second day of exercise, thereby providing significant insights into the onset and mechanisms of PEM.^{5,6,7,8} It is incorrect for the reviewers to say that 'experts have identified critical features of the condition including PEM, however current methods of testing, comparing, and monitoring this symptom are lacking'.¹ Even if these studies do not meet technical inclusion criteria, their findings begin to explain the poor and inconsistent results of exercise studies and to untangle the problem of heterogeneity by contributing to the identification of sub-groups, thereby addressing the aims of Key Questions 2a. b. and c.

If the aim of P2P and the Review is to advance thinking about 'ME/CFS', then it is sadly remiss in omitting evidence gleaned from biomedical studies. This approach can only lead to an imbalanced report and stifle future thinking and research into the condition. Surely, the AHRQ has an ethical duty not to risk the perpetuation of harms for patients by withholding important information from P2P.

The Review does not mention the dearth of studies of more severely affected patients, some of whom are house or bedbound. They cannot do exercise, let alone participate in exercise studies and so the conclusions of the Review, weak as they are, are skewed. For an insight into the effects of severe ME, I recommend the video 'Voices from the Shadows'.¹⁹ As noted in the Review, more severe cases are more likely to be identified by the International Consensus Criteria (ICC)⁹, not surprisingly, as these criteria are based on clinical examinations of thousands of patients by expert doctors. This is in contrast to the Oxford Criteria which rely mainly on fatigue.

Your Review states, '(We) recognize that some of the earlier criteria, in particular the Oxford (Sharpe, 1991)

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criteria, could include patients with 6 months of unexplained fatigue and no other features of ME/CFS. This has the potential of inappropriately including patients that would not otherwise be diagnosed with ME/CFS and may provide misleading results.’ and ‘Although most of the pharmacological trials were targeting an underlying pathophysiological dysfunction, most of the other interventions were targeting associated symptoms of the disease.’¹ Unfortunately, the authors only hint at this significant problem without exploring its implications for treating ME and CFS as synonymous terms. They also disregard the fact that the CBT/GET studies generally use the Oxford Criteria which refers to CFS, not ME.

The PACE authors recognise the difference in the conditions in noting that ‘The PACE findings can be generalised to patients who also meet alternative diagnostic criteria for chronic fatigue syndrome and myalgic encephalomyelitis but only if fatigue is their main symptom.’² It is unclear, however, if this caution is intended for patients with PEM. The results of PACE also cast doubt on this generalizability to ME.

Adherence to criteria in the studies is of importance but not guaranteed: the PACE trial intended to use the Oxford Criteria¹⁰ which does not include PEM. Yet, reportedly, 51% of subjects with PEM found their way into the trial, meeting the London criteria.² This loss of control of the sample characteristics has not been discussed by the PACE authors, who had an opportunity here to compare the PEM sub-group’s performance in the 6MWT with the performance of those without PEM. No mention of such an analysis is apparent in the reports.^{2,12}

As your Review point out, the CBT/GET trials purport to treat a different condition from biomedical studies which use criteria other than the Oxford. The PACE trial, in relation to GET, uses the ‘the deconditioning and exercise intolerance’ theories which ‘assume that the syndrome is perpetuated by reversible physiological changes of deconditioning and avoidance of activity’ with ‘increased perception of effort, leading to further inactivity.’² According to a further elaboration by the authors, CFS is ‘defined by a patient’s reported symptoms’, rather than objectively measured criteria.¹¹ In the CBT/GET studies such as PACE these are not ‘associated symptoms of the disease’, but the ‘disease’, which also involves patient attitudes thought to perpetuate the condition. The authors have not established the existence of such a condition, rather, this theory appears to be a favoured explanation, applied to a poorly diagnosed condition. While exercise intolerance is certainly part of ME, the reason for it is not ‘avoidance of activity’ – rather, avoidance of activity occurs because of intolerance of exercise. In a self-contradiction, ‘exercise intolerance’ does not form part of the Oxford Criteria, which is supposedly used here.

The PACE reports make no mention of the reversal expected by the theory, which apparently did not occur. Instead, in a follow-up report, there is a switch to the term ‘recovery’.¹² This paper illustrates how a definition of recovery has been constructed without regard to objective physical performance, as measured by the 6MWT. The definition itself has other problems.

This paper reports that 32 out of 144, or 22% of subjects ‘recovered’ after GET treatment. The composite criteria used for recovery includes the SF-36 score. In the course of the trial the threshold SF-36 score for recovery was changed from 85 to 60, lower than the score of 65 required at some points upon entry into PACE. (The original entry score was also changed from 60 to 65 mid-trial.) This made it possible to reach a ‘recovered’ score which was the same as or lower than the entry score.^{2,12} How many subjects relied on this lower score to be classified as ‘recovered’? How many reached the original post-treatment threshold score of 85? These figures are not reported.

Your Review also fails to mention the results of the 6 Minute Walking Test in PACE, the only objective test included in that trial.² In a sample of patients whose average age was 38 years, the best distance walked in six minutes reached a mean of 379 metres in the GET condition, a gain of 67 metres after 52 weeks of

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treatment. This is only 35 metres more than the specialist medical care (SMC)-only group. The CBT group showed no improvement compared with the SMC group². In other studies the 379 metres was exceeded by older patients with chronic heart failure, who managed 402 metres¹³ and by patients listed for lung transplantation.¹⁴ The PACE authors also refer to ‘concerns about patients with CFS coping with physical exertion’, the reason they were given no encouragement to walk faster in the final 6MWT¹¹, confirming the unrecovered state of the patients at the conclusion of PACE. Twenty-eight percent of patients for this test were lost to follow-up, more than for the self-report measures.¹¹

On the basis of these results the rejection of the PACE deconditioning hypothesis is indicated. The physiology-based CPET studies also contradict the deconditioning hypothesis. There is no discussion of this issue in the PACE reports.

The authors have refused to provide data which might validate the self-reports with the 6MWT results. How many patients who ‘recovered’ with a significantly improved SF-36 score also walked the distance expected from a recovered person? The absence of this data has been queried in correspondence published by Psychological Medicine,^{15,16,17} eliciting no satisfactory response from the authors who, instead, minimized the value of objective data for this condition¹¹. A Freedom of Information Request for this data was refused for different reasons at different times²⁰. Thus, evidence which should have been published, on which therapeutic policies are based, is being withheld. However, the authors have acknowledged that ‘objective measures of physical activity have been found previously to correlate poorly with self-reported out-comes’.¹²

The PACE trial fails to demonstrate useful effects on physical performance for ‘ME/CFS’ patients. Any conclusion of effectiveness of GET appear to rely on weak and ambiguous data and then only for a small number of patients, or data which has not yet been released. For further details of my critique of the PACE trial I draw your attention to my paper.¹⁸

The Review occupies itself with the results of a plethora of measures used in CBT and GET studies which sidestep the central issue of meaningful physical improvement from these treatments. It makes no contribution toward finding reasons for these failures, ignoring biophysical explanations which have been offered. GET is being imposed even as it is based on misconceptions about the physiological underpinnings of ME. The P2P must not be instrumental in continuing this situation.

The review and P2P need to acknowledge the failure of the CBT/GET model and its assumptions and to take seriously the harms recognized in the Review and further harms. They need to recognize and facilitate research into the discovery of the underlying biomedical factors. Accepting the ICC would be a good start.

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If the P2P had been asked to put stomach ulcers under a judge and jury model as you are doing for ME, you would have rejected the short course antibiotics intervention due to the length of the intervention and you would have definitely included papers pertaining to psychological- stress reduction- type A personality.

All the members on the panel will have a bias of some sort. Patients with ME encounter these characters on a regular basis. They are being told it's all in their heads, that they need CBT and GET. These physicians have learnt that from med school. This bias needs to be recognized. Most physicians have learnt to ignore patients with ME- for instance it is not a reportable disease. We do not usually or specifically die of ME. And while it can be fairly disabling, these physicians think this disease is not their department so said patients just drift away or disappear from that practice. It is safe to say that most physicians do not want such patients in their practice. The importance to recognize bias within the committee is crucial.

The reviewers have not noticed that the PACE trial had major issues with changing their protocol halfway into the trial so more people could be declared 'recovered'. This trial was simply propaganda, and yet Lancet published it. The authors refuse to release the raw data to be examined by members of the public. The point is they had a mix of patients in their trials, all you need to be included was to have fatigue for 6 months. Patients with ME have much more than fatigue and as you know, fatigue is prevalent with all diseases including rheumatologic conditions, cancer, HIV and depression.

You pointed on your report that all the definitions studied were about fatigue and that you were to study fatigue. I and many of my fellow patients want to tell you that the hallmark of our disease is not fatigue, but what is called post-exertional malaise, but even that name is insulting. I call it post-exertional relapse, or what Carruthers et al. call post-exertional neuro-immune exhaustion. This is what you need to focus on.

The P2P judge and jury model is using physicians who are not knowledgeable at all about ME, not knowledgeable about its history, the epidemics of the mid 1980's, the fact that CDC investigated the Incline Village epidemics and concluded that both patients and physicians were 'hysterical'. Therefore the panel starts with the bias of ignorance, and these panel members cannot be primed as of exactly what has happened in the last 30 years.

Our ME experts have lived through the bias of medical journals not wanting to publish their papers. They have lived through applying for NIH grants, or any government grants and unless the research was of psychological nature, they could not get such grants nor could they get support from their peers.

The impact for patients is isolation and stigma from the medical community at large. Patients have unbelievable unmet health care needs, and most of us have very clear stories of infectious trigger, without recovery. As you know, CBT does not treat HIV infections, or any other infectious process, including Ebola. GET has shown to harm ME patients. Patients do not want to be bedridden or housebound. It just happens to them because they are too sick to get out of their bed or their houses. and for those

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who are well enough to get out, they have learnt to pace themselves and to listen to their bodies so they don't relapse.

The P2P process has turned down or disregarded many many good papers relevant to the pathophysiology of ME and as a consequence, good science is being disregarded. The effect of this is that NIH will publish a paper discussing CBT and GET- when not one patient I know has recovered from their illness at all from CBT or GET. The harm it will do once more to the patient population is bigger than what P2P can realize because they are not cognizant of our history and political situation. All members of the panel needs to know that most prominent virus hunter professor Ian Lipkin (Columbia University) has been refused a NIH grant to research ME. Dr Lipkin received a 32 million \$ grant to research the micro biome, but not ME. What is it telling about the NIH grant review and its bias for ME? Judge and jury model does not work for us for grant review either. It was said somewhere that one of the reviewer for Dr Lipkin's grant felt that ME was psychological, therefore he didn't need to bother to search for infection.

We, the millions of patients around the world have been left behind and taken advantage of by the psychiatric lobby. This is not a mental illness. And yet the P2P is leaving behind the evidence, the one that is not good enough for your reviewers, and yet has been the best that our experts could do with the very limited amount of funding they had, and the very limited help they could get.

The danger of publishing a report such as the one you are preparing is enormous. You are damaging the patients, and their access to competent medical care. Some of us will commit suicide due to the lack of hope and lack of resources. Insurance companies will benefit from this report, using it to refuse claims.

I am sorry I cannot provide accurate and professional response and supporting my evidence by literature. I am a sick person and my brain does not function well, especially when in the vertical position. It is hard to make sense of that for most physicians, however patients in my community will nod in approval. Dysautonomia does this to patients. And I bet that no paper pertaining to dysautonomia has been reviewed.

What about the proteomics study showing abnormal proteins in CSF of patients with ME? Did you review that one? Probably not since the N= ? was too low.
<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0017287>

The question of definition on your report is muddling the whole field. You basically

Please do not fail patients, once more.

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It is unclear what is meant by "overlapping syndromes," but this seems to indicate a unique relationship between the stated diagnoses of ME/CFS, fibromyalgia, and depression (other diagnoses such as IBS are frequently cited in such a designation as well). This does not seem to be the case.

Such diseases can of course be comorbid, and it's true that other illnesses should be watched for, as comorbid diagnoses will frequently have treatment strategies which could reduce morbidity, but we have no sound data to indicate the kind of unique relationship that seems to be implied with the usage of "overlapping syndromes."

For example, fibromyalgia is known to occur as a common comorbid condition in lupus (22-25%), rheumatoid arthritis (25%), and Sjogren's (50%). [Bennet n.d.] Depression occurs in chronic diseases generally, possibly due in part to inflammation and other factors related to being ill [Voinov et al. 2013], and the rates of depression occurring in ME or CFS are similar to the rate of occurrence in other chronic illnesses, about 30-40% [Stein 2005], though this rate will vary based on how assessment is done, as some ways of assessment will classify symptoms of other illnesses as if due to depression (or anxiety, etc.) [Jerant 2014, Stein 2005, Blitshteyn 2009]. (As a side note, it seems that depression studies should also take care to stratify for or exclude ME/CFS, as some ME/CFS patients are diagnosed with depression without necessarily meeting any criteria for depression [e.g. Henderson 2014].) Besides these, some other examples of diagnoses noted to be comorbid with ME include Ehlers-Danlos syndrome, dysautonomia, Raynaud's, and asthma. [Underhill 2014, Raj and Rowe 2014].

Of course, many of these diagnoses, such as POTS, IBS, and asthma, have various diverse possible causes, with more causes remaining unknown [Raj and Rowe 2014, Lee & Park 2014, Ray et al. 2014]. While it's possible that a single pathology such as mast cell activation disease [Molderings et al 2011] or autoimmune disease [liME 2014] might underlie several comorbid conditions in a given patient, it is unlikely that any single explanation would explain the entire set of ME/CFS + fibromyalgia + IBS (or whatever lumped conditions were being considered together), given the diversity of physiopathologies being studied to subgroup the various diagnoses.

This sort of diversity of causes would be a logical working hypothesis to explain ME/CFS as well, and many leading researchers have taken an interest in subgrouping the illness [McGrath 2013, liME 2014].

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Comments on the AHRQ draft report on Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

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I offer here a few comments on the recently released preliminary draft of the AHRQ report on Diagnosis and Treatment of Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS).

First, I want to point to the intellectual absurdity of first admitting that ME and CFS may well describe different populations, and that definitions that do not make PEM mandatory may exacerbate this problem. And yet the authors go ahead and include all definitions on the same level. They then list their Key Questions, that intentionally omit all reference to attempts to understand the underlying processes of this disease/these diseases. They are interested only in Diagnosis and Treatment. But how can one arrive at an accurate Diagnosis without some understanding of the disease(s) being diagnosed? They set out to answer a question already made unanswerable before they begin. The whole project is premature and doomed, as many of us protested to NIH some time ago.

In the previously published “Background and Objectives for the Systematic Review” the authors report that “when patients were surveyed in April 2013 as part of the US Food and Drug Administration’s (FDA’s) patient-focused drug development initiative, treatments were divided into two broad categories, those intended to treat the underlying cause of the disease and those targeting specific symptoms. The first category included immune modulators such as rintatolimod (a.k.a. Ampligen) and rituximab, and antiviral and antibiotic medications.” Quite so—a proper distinction to make. They also state that “This report focuses on the clinical outcomes surrounding the attributes of fatigue, especially post-exertional malaise and persistent fatigue...because these are unifying features of ME/CFS that impact patients.” Again, quite proper—I like that word “unifying.” But what happened between those brave words and the completed Draft Report? That “unifying” has been withered to an “and/or,” so that definitions like the Oxford that do not include PEM, and qualify “fatigue” as simply a “subjective sensation” are allowed equal status with the CCC and ICC which do demand PEM as an essential symptom. That little word “or” makes a world of difference.

These changes make me wonder if there was rethinking or outside influence between the initial statement and the now published Draft. Whatever the case, the shift has been disastrous. It is accompanied by a list of reasons for “Inclusions” and “Exclusions” that prefaces the lamentably short list of “Included Studies” and the interminable list of “Excluded Studies,” which, in spite of brave statements about the inclusion of unpublished and other “grey” area texts, still excludes many important published and unpublished documents.

Those “Excluded” studies include key studies by VanNess, Snell and Stevens, and more recently by others that established the fact that a two-day VO2 Max test will, on the second test, show a marked fall in performance among ME patients that clearly demarcates them from others who also suffer from fatigue. This fact won’t go away, but it can be “disappeared,” and it seems it has been “disappeared” from this report, under Exclusion codes 9 and 3. Another good study, from Julia Newton’s Newcastle group, confirms the centrality of PEM from another angle—Jones D.E., et al, “Loss of capacity to recover from acidosis on repeat exercise in chronic fatigue syndrome: a case-control study.” It concludes that “when exercising to comparable levels to normal controls, CFS patients exhibit profound abnormality in bioenergetic function and response to it. Although exercise intervention is the logical treatment for patients showing acidosis, any trial must exclude subjects who do not initiate exercise as they will not benefit.” This study is excluded under Exclusion Code 8, “Wrong study design for a Key Question.” But the study in fact does contribute to the diagnostic toolkit that a physician could use, in my view. It also adds to the evidence for the centrality of PEM as a diagnostic criterion; all such studies seem to have been deselected or degraded in one way or another, whether by design or by coincidence is not clear.

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There is more. Cort Johnson in his latest piece on his website healthrising.com has dug out many important studies that were not even included in the “Excluded” category, but somehow completely overlooked—or passed by? Quite a few were, ironically, funded by NIH. They include four of the Lights’ gene expression studies, and Julia Newton’s important study of interaction between the ANS and peripheral muscle tissue under exercise. In fact, looking at this pattern, it seems almost as if a deliberate decision was made at some level to avoid or discard all studies that showed explicitly atypical biological responses to exercise in ME/CFS patients.

Such disturbed responses have now been made clear in numbers charted for exercise tests, and made graphically clear in gene and cytokine responses. They have objective, visible existence.

Science proceeds by formulating falsifiable hypotheses, which upon testing are either confirmed, altered, or falsified. The Oxford definition, which has been accepted on an equal footing with more recent, and better, definitions for this review, makes “fatigue” the “principle” and only required “symptom” for CFS. But this innocent looking word “symptom” has a very specific meaning within this definition, and I shall quote verbatim from the Oxford definition to emphasize my point here:

“When used to describe a symptom this is a subjective sensation and has a number of synonyms including, tiredness and weariness. ... The symptom of fatigue should not be confused with impairment of performance as measured by physiological or psychological testing. The physiological definition of fatigue is of a failure to sustain muscle force or power output.”

The wording is careful—though I disagree profoundly, the writers were not stupid or inarticulate—and I believe they meant and considered what they wrote. It is clear now that they were simply wrong in their definition of “fatigue” in ME/CFS, and that we now have many studies from different sources using different approaches that definitively falsify this hypothesis. There are measured tests of “impairment of performance”, whether we look at what happens when patients perform moderate exercise, or the highly stressful two day VO2Max test, which cannot be fudged. Since “fatigue” as “subjective sensation” is the central “symptom” of CFS in the Oxford definition, that definition has been falsified, and can no longer be legitimately used in research; studies that have used it must either be discarded, or placed in a separate category. To continue including them on a par with studies done under later and better (though still imperfect) definitions is to render the task of arriving at a better definition impossible. And that is what has happened here; there is no real answer to Key Question 1, and the decision to include all studies done under any definition on an equal basis made that impossible from the start, as indeed the opening discussion suggests as likely. This whole AHRQ exercise should be “Excluded” on the grounds they list as “8 Wrong study design for Key Question.”

The listings in this “Key” to these codes leads one to some serious absurdities, as in the case of the Mella and Fluge trial of Rituximab which was “Excluded” under Code 12, “Inadequate duration.” This is sheer irrelevance/absurdity—what counts is the effectiveness of an intervention, not how long it is applied before producing an effect; the application of this test elsewhere in medicine would exclude emergency heart surgery, joint replacement, a session of chemo for cancer, etc. etc. In fact, it took several months for the Rituximab infusion to produce results, and patients were followed for a long time, so that an intelligent understanding of the intervention would not have “disappeared” this trial at all. This little trial, very small as it admittedly was, has had a considerable effect on researchers in the field, focusing their attention on the probability that there is at the least an autoimmune (or autoinflammatory) component to ME, which aligns it further with MS. The authors’ comment that the synchronous improvement in all fields points to their having touched on a “central mechanism for the symptom maintenance” by depleting B cells should be taken very seriously as indicating a path to future research. Oddly enough, the authors of the Draft do assume that ME/CFS is a “relapsing and remitting” disease, which is part of their reason for demanding a certain length in a trial—but would they have used that phrase if the Mella and Fluge trial had never taken place? I doubt it. One can also fear that there is literal prejudice at work in the imposition of a minimal duration of intervention—medical interventions can be of very short duration, but behavioral interventions usually take time to work, and I suspect that there was a prejudgement that any really acceptable

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intervention would belong to the latter group—CBT or GET, in other words. Be that the case or not, it is fact that most of the purely “medical” interventions that have resulted in clear gains for at least some of the participants have been excluded, “disappeared,” under one code or another.

Back to another but related point. The earlier statement of intent cited above included the differentiation of intended outcomes for trials into “disease modifiers” and “symptom” modifiers. The Rituximab trial was one of rather few “disease modifiers”; others included the Ampligen (Rintatilomod) and the antiviral trials headed by Lerner, who has several papers. But most of Lerner’s papers are “disappeared” by Exclusion Codes; one is a Code 3—“does not address a Key Question.” This 2012 paper concludes that a very high % of a subset of ME patients manifest “a prolonged elevated antibody level against the encoded proteins EBVduTPase and EBV DNA polymerase,” suggesting quite strongly that these may constitute a subset of CFS patients. Why is the diagnosis of a possibly/probably definable subset within the overall disease not a valuable addition to the diagnostic toolkit for ME/CFS? An earlier Lerner paper from 2002 concluded that “16 CFS patients ...with EBV-persistent infection (EBV single- virus subset) are improved after 6 months of continuous pharmacokinetic dosing with valacyclovir. Nine CFS patients with EBV/human cytomegalovirus co-infection did not benefit from 6 months of similar treatment.” This is “disappeared” under Exclusion Code 7, “wrong outcomes.” Putting aside the general question of what “wrong outcomes” might possibly mean, in what way is this such an outcome? It supports the later suggestion that there is probably a subset of ME/CFS patients with persistent EBV infection who appear to improve with antiviral treatment. Is this not potentially very useful information for both diagnosis and treatment? Are there subsets visible within the ME/CFS community? It seems very possible, and these essays, and others showing the prevalence of ME/CFS after adolescent EBV mono also suggests that there are and that this is one of them. Why suppress this?

I will pass over the treatment of the PACE trial quickly because many have doubtless commented on the fact that despite claims to have looked at much out-of-the-way material, the team seems to have missed the important facts that besides being based on the Oxford definition, which includes depression and denies that CFS patients have more than a “subjective sensation” of fatigue—in spite of extensive research showing its very real existence—this trial claimed as “recovered” patients who still filled the requirement for entry. The authors have also gone to court to defend their refusal to release the original data of the trial, though such release is increasingly regarded as necessary for full validity. Despite all this, the PACE gets a moderate approval, though there is an overall reminder that all the trials considered for this review have some basic weaknesses.

I could go on, but will finish with a few comments on the use of EBM methodology in this case. Nigel T. James published a letter in *BMJ Clinical Research* (Aug 1996), close to the formal inauguration of EBM as a defined movement, from which I shall quote one paragraph: “Evidence based medicine seems to avoid all contact with first hand evidence by replacing original findings with subjectively selected, arbitrarily summarised, laundered, and biased conclusions of indeterminate validity or completeness. It has been carried out by people of unknown ability, experience and skills using methods whose opacity prevents assessment of the original data.” This is a rather irascible, intemperate response, but not without some application to the review discussed here.

There is no question that the EBM movement has had many successes, mostly in fields where there is a large body of published research on a defined intervention used in a clearly defined condition. It has improved treatment for some conditions, and has saved lives as a result. But there is also the growing feeling in some recent work, that critiques EBM and proposes new models such as “narrative reviews,” that EBM is running into serious problems, including the overwhelming of new lines of research by old and established criteria—remember that it took one doctor 20 years to overthrow the established model of how stomach ulcers are caused, 20 years and 3 inflictions of a bacteria infection upon himself. I fear that something like that is happening here. New lines of thought and research are buried or “disappeared” under the weight of studies done largely under definitions that I have argued above have now been thoroughly falsified; EBM can represent the dead hand of the past strangling the birth of the new and more accurate.

The NIH seems to have declared war on the ME/CFS community—researchers, patients and advocates

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together—in rebuffing their protests and suggestions for better lines of action, and imposing their own models, that throw much of the work onto the shoulders of people who know nothing or very little about the condition. The declaration of war was always shrouded in seemingly friendly words, but the intent was made clear enough through action—the heavy weight of bureaucratic power was constantly present, refusing real input, spending money on the IOM and AHRQ while refusing it to Ian Lipkin, etc. With the publication of this Draft (it may be revised a little, but I foresee no major shifts) the gloves seem to be off. One fears that the moment of a “final solution” may be at hand, and I have no idea what that may lead to.

WellPoint has already declared that they will no longer pay for autonomic nervous system testing in ME/CFS, despite all the recent research showing that it is indeed a central player in the condition. What else may follow? I have no idea. I dread what may happen if and when this AHRQ document is given into the hands of a “jury” that explicitly excludes those who know something. Advances in understanding and treating this debilitating and costly—to both patients and society—condition will not come from the NIH under its present mode of operating.

I am sorry that your group has lent itself to use in this way and has produced such an unhelpful report, though that was inherent in the request itself. Your energies and experience could doubtless have been better employed in other areas.

Sincerely,

Christopher Heppner,
Ph.D. Victoria, BC, Canada

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To: AHRQ reviewers-P2P workshop for ME/CFS
Scientific Resource Center
Portland VA Research Foundation

Date: 10/20/2014

Re: Comments on the AHRQ Draft report on Diagnosis and Treatment of Myalgic
Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS)

To begin, I want to state my overall opposition to the Pathways to Prevention Workshop as a strategy to address research gaps in ME/CFS. My objection is based on the following:

1. The use of non experts to review and interpret the research. ME/CFS is a complex disease that is poorly understood by general practitioners and researchers. There are a handful of experts who have been involved in clinical practice and/or research who would be much better at providing interpretation and recommendations for future research. The deliberate use of “non experts” via a “jury model” coupled with the void of large scale robust research, due to significant underfunding, seems unfair at best and at worst appears to be a deliberate attempt by HHS/NIH to squelch further research into identification of biological causes and treatment.
2. The lack of a standardized definition used in both clinical diagnosis and research thus far that does not allow for separation of people with the main symptoms of post-exertional exacerbation of symptoms, neurocognitive, autonomic and immune dysfunction etc. from people who are just tired, or depressed, like the Oxford criteria used by the PACE trial. It also makes it very difficult to compare studies against one another to aid in answering the P2P questions as the populations studied cannot be assumed to be the same and therefore conclusions should be suspect. For case definition, I recommend that the P2P support the [50 experts](#) and [66 advocates](#) that have asked the former HHS secretary to adopt the Canadian Consensus Criteria.
3. There simply was no need for HHS/NIH to commission the P2P project, instead, they could have just honored requests made throughout the 10+ year history of the [Chronic Fatigue Syndrome Advisory Committee \(CFSAC\)](#). A congressional initiative currently underway called the [21st Century Cures Initiative](#), has produced a common theme arising from roundtable meetings around the country. The theme is about involving patients in setting the research agenda for NIH, academia, industry and consortia. With its’ patient/advocate members, clinical experts and government official representation, CFSAC could be a prime example for how to involve key stakeholders in developing a research agenda. But instead of listening to CFSAC, HHS/NIH commissioned the P2P project which seems to be working in direct opposition of patient/expert involvement. Like the saying, “if you are not at the table you are probably on the menu”, it sure feels like ME/CFS patients are being served up on the chopping block by the P2P process.

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4. The P2P questions are wrong and seem to have been changed from the original to something too narrow in scope. If the AHRQ report is any indication of the direction to be taken by the P2P it appears to be deliberately biased in favor of behavioral interventions while eliminating non-behavioral based etiologic/treatment research and disregarding the major issue of multiple case definitions. As a result, the only possible outcome from the P2P process is likely to be a bad one for ME/CFS patients resulting in possible harm due to mistreatment and/or financial hardship because of insurance and disability benefit denials and continued prejudice and stereotyping by health providers, the media and the general public.

Comments on specific statements in the AHRQ report

AHRQ report: Pg. ii 3rd paragraph

Comments: This paragraph should be stricken. The purpose of this report is to support the Pathways to Prevention Workshop for “Advancing the research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome”. This report should not be used for “clinical guidelines” or as a “basis for reimbursement or coverage policies”.

AHRQ report: Page v. Paragraph on “Results” states: “A diagnosis of ME/CFS is associated with broad psychosocial consequences.” And conclusions on pages vi and 80 state that “GET appears to be associated with harms in some patients **whereas the negative effects of being given a diagnosis of ME/CFS appear to be more universal.**”

Comments: These statements are incorrect and are not supported by the information presented on page 19 regarding the “Key Question 1c- What harms are associated with diagnosing ME/CFS?” They should be deleted or revised.

The statements noted above make it appear that being given the diagnosis creates issues for ME/CFS patients. While it is true that most ME/CFS patients do not like the name “Chronic Fatigue Syndrome” and most would prefer that the illness be called “Myalgic Encephalomyelitis”, it is not the diagnosis itself that raises issues. Most patients actually report relief once they have been given a diagnosis for their disabling symptoms. It is the symptoms that lead to disability which in turn impacts employment, ability to attend school and participate in activities of daily living. Also, as correctly stated on page 19 of the Report, prejudices and stereotypes held by healthcare professionals and spread by the media are influenced by the name “Chronic Fatigue Syndrome” as well as treatment recommendations for CBT/GET which imply that ME/CFS is a psychological based disorder versus the biological based disorder that patients know it is.

General Comments about Methodologies and Summaries in the AHRQ Report

Clinical and Research Definitions

There is an overall failure to identify what disease is being studied by the P2P panel. In the AHRQ report, eight case definitions are identified and while the report acknowledges this as an issue, it still goes on to answer the questions about subgroups, diagnostics, treatments and harms for all CFS and ME patients based on studies done using any of these eight definitions. In doing so, the Report ignores its own conclusion regarding the differences in populations tied to multiple case definitions. Basically, it cannot be concluded that the same disease is being studied when you apply all of the 8 criteria. It seems unconscionable

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that this was allowed to happen in the Report and has significantly influenced the acceptance of some studies (e.g. PACE study using the very problematic Oxford definition) while other reports using more the rigorous and more accepted criteria (ICC, CCC) were excluded.

Counseling and Behavioral Therapies (pg 46)

The AHRQ report seems to favor studies for CBT and GET and has rated several of them “good” despite many data flaws and difference in case definitions. Meanwhile, studies showing abnormal and sometimes harmful response to exercise are excluded and although the report indicates that it is possible that CBT and GET could be harmful, it does not make that conclusion. I’ve noticed in AHRQ reports on other topics that pharmacological studies sponsored by pharmaceutical companies are often faulted for potential bias, yet behavioral based intervention studies conducted by mental health clinicians, whose livelihood depends on providing these treatments, are not criticized as being biased. The Report should be amended to mention the potential bias related to counseling and behavioral therapies.

The PACE trial (White, *et al.*, 2011) 98, is one of the few treatment trials to receive a “good” rating, and it is froth with methodological issues. The issues include:

1. The PACE trial used the Oxford definition, which the AHRQ report notes can be problematic in that it included people with idiopathic fatigue and primary depression who most likely do not have ME/CFS.
2. Patient performance on the “6-minute walking test” at the end of the trial showed no significant improvement and results are indicative of continued severe functional impairment on the level of someone with heart failure. For an comprehensive analysis of this component of the PACE study, I recommend this article by Susanna Agardy (Australia), [“‘Recovery’ in PACE, the 6 Minute Walking Test and Other Issues: How Well Can ‘Recovered’ Patients Walk?”](#)
3. **Due to changes in the methodology after the conclusion of the study someone could enter the trial with a SF-36 physical function score of 65 and end with a score of 60 and be considered “recovered”.** So people who scored lower after the intervention was completed were considered to be cured, huh? Putting methodology issues aside, it should also be noted that an SF-36 score of 60 would be comparable to someone with early stage heart failure, and since the average age of the participants in the study was 39 years, that alone should be raising red flags. A subsequent publication using the PACE data called [“Recovery from chronic fatigue syndrome after treatments given in the PACE trial” published by the authors of the PACE trial in Psychol Med in October 2013 \(43\(10\): 2227–2235\)](#), acknowledges the post-hoc methodology changes in the study. Oddly, this paper is not even mentioned in the AHRQ report. The above points should cause significant concern over the methods and analysis used in this study.

In summary, the PACE trial has been one of the most disputed trials in ME/CFS research history. Much of these disputes can be found in the form of letters to the editors and other published articles that were not included in the AHRQ search. Freedom of information requests asking for the raw data from the trial to be made available for outside analysis have been repeatedly denied. Some speculate that PACE, one of the few ME/CFS studies to receive significant funding by the UK government, was performed with an ulterior motive of the NHS to limit health coverage and access to disability benefits for ME/CFS patients in the United Kingdom. There is acknowledgement of conflicts of interest of several of the studies investigators in the published study that could help to

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substantiate that claim and there is obvious bias by the researchers who have a financial interest in promoting behavioral interventions

Because of the definition, methodological issues, biases and conflicts of interest, the overall rating for the PACE study should be downgraded from good to poor, or better yet this study should be excluded from the analysis.

Excluded and omitted studies:

It appears that some important studies with major implications for advancing clinical biomarkers and treatment modalities were excluded or omitted from the report. Many of these studies were done by well regarded NIH grant awarded researchers so it is bewildering how this could happen. The short comment period for this draft report precludes most of us from doing a thorough review of the literature and comparison to identify omitted studies, furthermore, the information provided in the report is not sufficient to explain why some studies were excluded. With an overall exclusion rate of 90% it appears that the exclusionary criteria for many of these studies were much too harsh and should be re-evaluated. Some areas of specific concern include:

1. **The exclusion of biomarker and other research that could aid in objective diagnosis because they were considered by AHRQ to “be intended to address etiology”, which was not within the scope of the P2P questions. It is not clear on the rationale for this. One of the biggest concerns for advancing ME/CFS research and treatment revolves around the understanding of the etiology of the disease and development of biomarkers to aid in diagnosis and to provide targets for treatment. This decision should be re-evaluated.**
2. **Twenty-five studies were eliminated because they had the wrong study design, which included case control studies, letters to the editor, small sample size and non-comparative studies. It appears that only randomized trials were acceptable in regards to study design. Again, I think it should be noted how poor funding for ME/CFS research impacts the ability to carry out robust randomized trials with large sample sizes. It is not clear why AHRQ did not accept case-control studies for their review in light of the vast number of excluded studies. I recommend that this be reconsidered.**
3. **Some studies were eliminated because they failed to do the types of analysis required by the AHRQ. This also seems completely unfair and more effort should be given to further review these studies for their potential inclusion in the discussion. Like previously noted, ME/CFS research funding has been abysmal for 30 years, which means that many of the studies that are completed are done so on very small budgets which limit sample size and complicated analysis. It simply is not fair to put these studies aside and not use them to inform decisions about funding future research.**
4. **Treatment studies required 12 weeks of treatment to be included in the Review. This decision should be evaluated to take into consideration clinical standards of practice for the particular treatment modalities. For example, a study on rituximab ([Fluge O, Bruland O, Risa K, et al. Benefit from B-lymphocyte depletion using the antiCD20 antibody rituximab in chronic fatigue syndrome. A double-blind and placebo-controlled study. PLoS ONE. 2011;6\(10\):e26358. PMID: 22039471](#)), was excluded because the treatment phase was less**

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than 12 weeks. If one was to look at the recommended administration of rituximab for other FDA approved conditions you would see that the Fluge study followed protocols comparable to these other conditions. Treatment with rituximab over 12 weeks is not standard practice and it could be harmful. Therefore, this study should be included in the review. Similar issues are likely to have affected other medication based studies, such as those studying antiviral medications which are often prescribed for periods of less than 12 weeks. This reason for exclusion should be re-evaluated for medication treatment studies and studies that were eliminated should be re-considered.

For a list of excluded studies that should be evaluated, please see Attachment 1.

For a list of studies that were not included or exclude, please see Attachment 2.

Summary

In summary, information and conclusions outlined in the draft AHRQ Report seem to provide little help for the P2P workshop to accomplish its' goal of "Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome". By contrast it looks like it is setting the stage to do the opposite, as it is more than likely to result in promotion of psychological and behavioral interventions that ME/CFS patients say **do not** help to reduce symptoms and disability, and for some, have actually caused progression of the illness. The notation in the Report that it may be used for clinical guidelines and coverage decisions is also particularly concerning. It appears that HHS is looking to provide fuel for the insurance industry, Medicare/Medicaid and Social Security to deny coverage for medical and disability benefits for ME/CFS patients, similar to what has happened in the United Kingdom.

Missing from the report is data on NIH funding for ME/CFS which is critical to the P2P discussion. Affecting an estimated 1 million plus people in the US, ME/CFS receives around 5 million dollars annually for research or roughly \$1.56 per affected life per year versus HIV affecting the same number of people, which receives closer to \$25,000 per patient per year. Yet due to treatments available to HIV patients, patient disability is actually higher in ME/CFS and is comparable to end stage AIDS. Several highly profiled and respected researchers in the U.S. from institutions like [Columbia](#) and [Stanford](#) have been denied NIH funding for ME/CFS, yet they receive large grants for other projects, why is that?

Also missing from the report is how the disease affects children and adolescents as well as comprehensive morbidity and mortality information on the disease. There is no information about the degree of disability and progressive nature of the disease that has low (<10%) reported "true" recovery rates, not those alleged by PACE with their manipulated data. Studies on the severely disabled, homebound/bedbound population, estimated to be up to 25% of people in the U.S. with ME/CFS, are missing from the research which is a huge void that needs to be addressed. Early mortality is another important issue that is not addressed in the Report. The average age of death is reportedly lower than the general population due to higher rates of cancer, progressive disease and suicide. Post mortem examination is rare, even when bodies are willed to science, due to lack to systems to support these requests.

The AHRQ Report must address the above issues, whether they are within the scope of the project or not, if it is to provide a well rounded **unbiased** view of ME/CFS. To gain a better understanding of the impact of this illness on patients, I recommend that the following be to the AHRQ writers and the P2P panel members:

- The [Voice of the Patient report](#) issued by the FDA in 2013
- The film, [Voices from the Shadows](#) full length film that can be viewed for \$3.00.
- The [National CFIDS Foundation "In Memoriam"](#) list of people with ME/CFS that have died

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Finally, President Barack Obama wrote [“My Administration is committed to creating an unprecedented level of openness in Government. We will work together to ensure the public trust and establish a system of transparency, public participation, and collaboration. Openness will strengthen our democracy and promote efficiency and effectiveness in Government.”](#) Where is the transparency, openness and encouragement of public participation in this P2P process? Clearly from recent documents revealed via a FOIA request, there was no desire for that to happen.

Acknowledgements

I want to acknowledge that parts of my response were based on information posted on the following blog sites: [Occupy CFS](#) , [Health Rising](#), and [Onward Through the Fog](#). I wish to thank all of the writers of these blogs for their thorough review and comments on the AHRQ Draft Report.

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Attachment 1

Important Excluded Studies that should be re-evaluated:

(Note- most of these were taken from the Health Rising Blog titled "[AHRQ Report – Excluding Progress? The Exclusionary factors and Missing Studies](#)")

Study	Exclusion Reason	Comment
<p>Immunological abnormalities as potential biomarkers in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. Brenu EW¹, van Driel ML, Staines DR, Ashton KJ, Ramos SB, Keane J, Klimas NG, Marshall-Gradisnik SM. J Transl Med. 2011 May 28;9:81. doi: 10.1186/1479-5876-9-81.</p>	#2	An immunological biomarker study that found differences in NK cells and immune function in patients with ME/CFS
<p>Markers of inflammation and immune activation in chronic fatigue and chronic fatigue syndrome. Buchwald D¹, Wener MH, Pearlman T, Kith P. J Rheumatol. 1997 Feb;24(2):372-6.</p>	#2	Study looked at inflammation markers
<p>Brain 5-HT1A receptor binding in chronic fatigue syndrome measured using positron emission tomography and [11C]WAY-100635. Cleare AJ¹, Messa C, Rabiner EA, Grasby PM. Biol Psychiatry. 2005 Feb 1;57(3):239-46.</p>	#2	Serotonin receptor binding study that found differences between health controls and CFS patients.
<p>Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome. Demitrack MA¹, Dale JK, Straus SE, Laue L, Listwak SJ, Kruesi MJ, Chrousos GP, Gold PW. J Clin Endocrinol Metab. 1991 Dec;73(6):1224-34</p>	#2	Cortisol study that found at differences between ME/CFS patients and controls.

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Study	Exclusion Reason	Comment
<p>Impaired cardiac function in chronic fatigue syndrome measured using magnetic resonance cardiac tagging.</p> <p>Hollingsworth KG¹, Hodgson T, Macgowan GA, Blamire AM, Newton JL. J Intern Med. 2012 Mar;271(3):264-70. doi: 10.1111/j.1365-2796.2011.02429.x. Epub 2011 Aug 15.</p>	#2	Study that found impaired cardiac function in ME/CFS
<p>Gene expression subtypes in patients with chronic fatigue syndrome/myalgic encephalomyelitis.</p> <p>Kerr JR¹, Petty R, Burke B, Gough J, Fear D, Sinclair LJ, Mattey DL, Richards SC, Montgomery J, Baldwin DA, Kellam P, Harrison TJ, Griffin GE, Main J, Enlander D, Nutt DJ, Hoggate ST. J Infect Dis. 2008 Apr 15;197(8):1171-84. doi: 10.1086/533453.</p>	#2	Gene expression subtype study
<p>Discriminative validity of metabolic and workload measurements for identifying people with chronic fatiguesyndrome.</p> <p>Snell CR¹, Stevens SR, Davenport TE, Van Ness JM. Phys Ther. 2013 Nov;93(11):1484-92. doi: 10.2522/ptj.20110368. Epub 2013 Jun 27</p>	#2	Use of a 2 day exercise test showed ability to distinguish ME/CFS patients from controls with 95% accuracy
<p>Loss of capacity to recover from acidosis on repeat exercise in chronic fatigue syndrome: a case-control study.</p> <p>Jones DE¹, Hollingsworth KG, Jakovljevic DG, Fattakhova G, Pairman J, Blamire AM, Trenell MI, Newton JL. Eur J Clin Invest. 2012 Feb;42(2):186-94. doi: 10.1111/j.1365-2362.2011.02567.x. Epub 2011 Jul 12.</p>	#8	Exercise study showing inability to recover from acidosis post exercise
<p>Influence of exhaustive treadmill exercise on cognitive functioning in chronic fatigue syndrome.</p> <p>LaManca JJ¹, Sisto SA, DeLuca J, Johnson SK, Lange G, Pareja J, Cook S, Natelson BH Am J Med. 1998 Sep 28;105(3A):59S-65S</p>	#8	It's not clear why this study was not included. It concluded that ME/CFS patients show cognitive impairment after exercise vs. controls.
<p>Fluge O, Bruland O, Risa K, et al. Benefit from B-lymphocyte depletion using the antiCD20 antibody rituximab in chronic fatigue syndrome. A double-blind and placebo-controlled study. PLoS ONE. 2011;6(10):e26358. PMID: 22039471</p>	# 12	Treatment study excluded due to length of treatment— NOTE: it would be contraindicated, and possibly harmful to administer Rituximab for 12 weeks.

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Attachment 2

Studies that were not included or excluded that should be evaluated include the following:
(Note- these were taken from the Health Rising Blog titled "[AHRQ Report – Excluding Progress? The Exclusionary factors and Missing Studies](#)")

[J Behav Neurosci Res. 2010 Jun 1;8\(2\):1-8. A Comparison of Immune Functionality in Viral versus Non-Viral CFS Subtypes. Porter N1, Lerch A2, Jason LA, Sorenson M, Fletcher MA, Herrington J.](#)

[Cytokine expression profiles of immune imbalance in post-mononucleosis chronic fatigue. Broderick G, Katz BZ, Fernandes H, Fletcher MA, Klimas N, Smith FA, O’Gorman MR, Vernon SD, Taylor R. J Transl Med. 2012 Sep 13;10:191. doi: 10.1186/1479-5876-10-191.](#)

[Exercise responsive genes measured in peripheral blood of women with chronic fatigue syndrome and matched control subjects. Whistler T, Jones JF, Unger ER, Vernon SD.](#)

[A Chronic Fatigue Syndrome – related proteome in human cerebrospinal fluid. Baraniuk JN, Casado B, Maibach H, Clauw DJ, Pannell LK, Hess S S. BMC Neurol. 2005 Dec 1;5:22.](#)

[Differences in metabolite-detecting, adrenergic, and immune gene expression after moderate exercise in patients with chronic fatigue syndrome, patients with multiple sclerosis, and healthy controls. White AT, Light AR, Hughen RW, Vanhaisma TA, Light KC.](#)

[Genetics and Gene Expression Involving Stress and Distress Pathways in Fibromyalgia with and without Comorbid Chronic Fatigue Syndrome. Light KC, White AT, Tadler S, Iacob E, Light AR.](#)

[Severity of symptom flare after moderate exercise is linked to cytokine activity in chronic fatigue syndrome. White AT, Light AR, Hughen RW, Bateman L, Martins TB, Hill HR, Light KC.](#)

[Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects. Light AR, White AT, Hughen RW, Light KC. Psychosom Med. 2012 Jan;74\(1\):46-54. doi: 10.1097/PSY.0b013e31824152ed. Epub 2011 Dec 30.](#)

[Cerebral vascular control is associated with skeletal muscle pH in chronic fatigue syndrome patients both at rest and during dynamic stimulation. He J, Hollingsworth KG, Newton JL, Blamire AM.](#)

[Clinical characteristics of a novel subgroup of chronic fatigue syndrome patients with postural orthostatic tachycardia syndrome. Lewis I, Pairman J, Spickett G, Newton JL.](#)

[Chronic fatigue syndrome and impaired peripheral pulse characteristics on orthostasis—a new potential diagnostic biomarker. Allen J, Murray A, Di Maria C, Newton JL.](#)

[Physiol Meas. 2012 Feb;33\(2\):231-41. doi: 10.1088/0967-3334/33/2/231. Epub 2012 Jan 25. Chronic fatigue syndrome and impaired peripheral pulse characteristics on orthostasis—a new potential diagnostic biomarker. Allen J1, Murray A, Di Maria C, Newton JL.](#)

[Increased d-lactic Acid intestinal bacteria in patients with chronic fatigue syndrome. Sheedy JR, Wettenhall RE, Scanlon D, Gooley PR, Lewis DP, McGregor N, Stapleton DI, Butt HL, DE Meirleir KL. In Vivo. 2009 Jul-Aug;23\(4\):621-8.](#)

[Responses to exercise differ for chronic fatigue syndrome patients with fibromyalgia. Cook DB, Stegner AJ, Nagelkirk PR, Meyer JD, Togo F, Natelson BH. Med Sci Sports Exerc. 2012 Jun;44\(6\):1186-93. doi: 10.1249/MSS.0b013e3182417b9a.](#)

[Med Sci Sports Exerc. 2005 Sep;37\(9\):1460-7. Exercise and cognitive performance in chronic fatigue syndrome. Cook DB1, Nagelkirk PR, Peckerman A, Poluri A, Mores J, Natelson BH.](#)

[Regional grey and white matter volumetric changes in myalgic encephalomyelitis \(chronic fatigue syndrome\): a voxel-based morphometry 3 T MRI study. Puri BK1, Jakeman PM, Agour M, Gunatilake KD, Fernando KA, Gurusinghe AI, Treasaden IH, Waldman AD, Gishen P.](#)

[Unravelling intracellular immune dysfunctions in chronic fatigue syndrome: interactions between protein kinase R activity, RNase L cleavage and elastase activity, and their clinical relevance. Meeus M, Nijs J, McGregor N, Meeusen R, De Schutter G, Truijien S, Frémont M, Van Hoof E, De Meirleir K. In Vivo. 2008 Jan-Feb;22\(1\):115-21.](#)

[Detection of herpesviruses and parvovirus B19 in gastric and intestinal mucosa of chronic fatigue syndrome patients. Frémont M, Metzger K, Rady H, Hulstaert J, De Meirleir K. In Vivo. 2009 Mar-Apr;23\(2\):209-13.](#)

[J Psychosom Res. 2006 Jun;60\(6\):559-66. Impaired natural immunity, cognitive dysfunction, and physical symptoms in patients with chronic fatigue syndrome: preliminary evidence for a subgroup? Siegel SD1, Antoni MH, Fletcher MA, Maher K, Segota MC, Klimas N.](#)

[Neuroimage. 2005 Jul 1;26\(3\):777-81. Epub 2005 Apr 7. Gray matter volume reduction in the chronic fatigue syndrome. de Lange FP1, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, Toni I.](#)

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[Neuroimage. 2005 Jun;26\(2\):513-24. Epub 2005 Apr 7. Objective evidence of cognitive complaints in Chronic Fatigue Syndrome: a BOLD fMRI study of verbal working memory. Lange G1, Steffener J, Cook DB, Bly BM, Christodoulou C, Liu WC, DeLuca J, Natelson BH. Appl Neuropsychol. 2001;8\(1\):23-30.](#)
[Quantitative assessment of cerebral ventricular volumes in chronic fatigue syndrome. Lange G1, Holodny AI, DeLuca J, Lee HJ, Yan XH, Steffener J, Natelson BH. PLoS One. 2011 Feb 23;6\(2\):e17287. doi: 10.1371/journal.pone.0017287.](#)
[Distinct cerebrospinal fluid proteomes differentiate post-treatment lyme disease from chronic fatigue syndrome. Schutzer SE1, Angel TE, Liu T, Schepmoes AA, Clauss TR, Adkins JN, Camp DG, Holland BK, Bergquist J, Coyle PK, Smith RD, Fallon BA, Natelson BH.](#)

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Firstly, a brief apology for not being as thorough and well researched in my comments as I would like, and the clumsy structure of my response. I have only been able to look in detail at a couple of areas, and I am concerned that the limited time provided for comments on this draft may lead to important issues going unaddressed.

I hope that this is only the beginning of a process which will provide further time for discussion and debate as the review develops. The political and social context around ME/CFS needs to be addressed, particularly as part of any attempt to assess the costs and benefits of biopsychosocial approaches to the management of patients, and this requires extra work and care from those conducting any review, certainly in comparison to an assessment of the efficacy of a pharmaceutical intervention which can be assessed in double-blind trials.

“Given the breadth of symptoms in ME/CFS, we a priori elected to not review symptom related outcomes except for fatigue.” (Draft review, es30)

A problem with this is the we do not have a reliable measure for ‘fatigue’. Much trouble has been caused by researchers seeming to just assume some fatigue questionnaire reliably captures the symptom most troubling to patients with ME/CFS, even when assessing biopsychosocial interventions specifically intended to alter patient cognitions.

Earlier in the history of the biopsychosocial management of ME/CFS, it was recognised that other more objective outcomes were of importance. A 1990 letter from Wessely et al. recognised that an increase in patient’s activity must ultimately be the aim of any treatment [1], while a later Wessely et al. response to an RCT [2] which found CBT to be no more effective at increasing self-reported activity than placebo (this study was given exclusion code 9 in the draft review, despite being a rare biopsychosocial study with a placebo control) stated that “the primary aim of treatment is to restore activity and function” and “if a patient completes the program, he or she must have increased their activity, even if everything else remains unchanged.”[3] It was therefore argued that the efficacy of CBT had not truly been tested as the patients “may have attended the sessions, but did not comply with the program”.

Such claims are now rarely made by those who have developed and promote CBT as an effective treatment for CFS. In 2001 an RCT assessing CBT for CFS was published in the Lancet [4] reporting a positive result for patient’s self-reported fatigue and functional impairment. Although not released at the time, the trial also collected actimeter data, which found that in this ‘positive’ trial CBT did not lead to patients being able to increase their activity levels. This finding was repeated in two further trials [5,6] and then finally the data was released in a 2010 meta-analysis [7], where the results were presented as evidence that CBT is effective even without patients needing to increase their activity levels. This actimeter data has also been excluded from the draft review.

Although the PACE trial [8] had listed actimeters as an outcome measure in the trial’s identifier, and then purchased and used them at baseline, they were later dropped as an outcome measure.[9] In his response to concerns about the lack of objective outcome measures, Professor White stated “We have used several objective outcome measures; the six minute walking test , a test of physical fitness, as well as occupational and health economic outcomes”.[9] The addition of CBT to patient’s medical care did not lead to improvements in any of the objective outcome measures, while the addition of GET led to a statistically significant improvement only for the six minute walking test, with this improvement failing to reach the criteria for clinical significance used for other outcome measures in the trial.

It is important that evidence is collected and assessed independently of the preferences of those researchers who may have ideological, professional or financial interests in the promotion of particular treatments. Data from the above trials showing no improvement in activity levels [7] and neuropsychological performance [10] should be assessed and fed into the findings of this review, even if it is presented in a way which would allow it to be excluded. The decisions to class questionnaire scores as outcome measures, and objective measures of activity as merely a way of assessing mediators of efficacy merely reflects the preferences of the researchers involved, and one could just as easily choose to present things the other way around.

Where results from subjective and objective outcome measures diverge it is no more reasonable for researchers to decide amongst themselves that biopsychosocial interventions tested in non-blinded trials should be assessed primarily via subjective self-report measures than it would be if they were testing Chakra balancing healing or anything else. It is important that claims about the efficacy of treatments are based upon good and reliable evidence, or else those with health problems can find themselves losing their lives to health interventions whose efficacy has been misrepresented to them. I do not believe that most patients would see an intervention which allowed them to fill in questionnaires more positively, but not actually perform any more activity, to be genuinely effective. It seems that the developers of CBT for CFS formerly agreed.

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Biopsychosocial rehabilitative approaches take considerable time and effort, and whenever claims about their efficacy are based upon non-blinded trials and subjective self-report measures it is important the the potential problems with response bias are clearly explained. When discussing the evidence that CBT and GET improve symptoms on page 76 (122 of pdf) the only reference to the problems with self-reporting relate to adherence. In order to use the available evidence to claim that CBT and GET improve patient's symptoms, one first need to provide good evidence that the questionnaires used in these non-blinded trials are reliable measures of patient's symptoms (which the review recognises has not been done) - without this, it should only be claimed that CBT and GET can lead to patients describing their symptoms more positively on questionnaires.

While I have not been able to look closely at this, I am also concerned that the draft review seems to make exaggerated claims about the value of CBT for improving employment. The PACE trial was reported in the review as showing improvement, yet in one of the PACE trial's papers they reported that "there was no clear difference between treatments in terms of lost employment", and "receipt of benefits due to illness or disability increased slightly from baseline to follow-up" [11]. It cannot be right to assess employment outcomes via WSAS scores rather than the measured employment outcomes.

Also, while this report is in French, a review of Belgium CFS clinic providing biopsychosocial rehabilitative approaches is available here: <http://www.inami.fgov.be/care/fr/revalidatie/general-information/studies/study-sfc-cvs/index.htm> As well as providing information on the efficacy of these interventions in a setting outside of medical trials, this assessment also has the advantage of having been conducted by those without a vested interest in making positive claims about the value of CBT/GET. This report again finds that the interventions assessed did not lead to improvements in employment outcomes. Results from the CFS/ME National Outcomes Database have also been published [12], this time by those involved in running the centers assessed. Results showed that centres providing CBT/GET seemed to perform less well than those providing just 'activity management', and with all performing less well on the self-report measures used than we saw in the recently reported PACE trial [8,13].

We are currently lacking good evidence that biopsychosocial rehabilitative approaches are more effective than placebo, Chakra healing, or any other intervention that leaves patients wanting to be positive to their therapist and that is assessed via self-report measures. It is important that this is made clear so that patients are able to make informed decisions about their own medical care and their own lives.

There is considerable concern from patients that one of the side-effects of the medicalisation of the psychosocial aspects of ME/CFS patient's lives is that some medical staff see this as an excuse to take it upon themselves to manipulate patients as they see fit, without informed consent. There does seem to be a problem with unduly positive claims made about the efficacy of treatments and the likelihood of recovery, with this leading to understandable anger and distrust.

I think that aspects of these problems can be seen in two biopsychosocial trials that the draft review has assessed as being of good quality. In the FINE trial [14] patients were encouraged to adopt a range of positive cognitions, this involved 'Rousing Reassurance' such as:

From the moment you walk out of this room your recovery is beginning.
There is no disease
Go for 100% recovery. [15]

Unsupported claims were made about the reversible nature of patient's condition were made to patients and medical staff. While the treatment itself was shown to be ineffective, even at improving patient's questionnaire scores, unsurprisingly the cognitions promoted still had an impact, and led to further unreasonable assumptions being made. The views of some specially trained nurses was summed up (in a paper which seemed unconcerned by the ineffective nature of the treatment being provided) with the quote: "The bastards don't want to get better". [16]

Despite the poor results of the FINE trial, and the prejudices promoted by the nature of the intervention, Alison Weardon still describes her involvement in this trial and the development this treatment for CFS as being the proudest moment of her career.[17] I believe that this help illustrate a problem with ideological and emotional conflicts of interest that are commonplace in ME/CFS research. A recent Cochrane editorial reported what should be "a cardinal rule: the need to separate the clinical evaluation of innovations from their innovators, who irrespective of any of their endeavors to be 'neutral' have a substantial investment, whether emotional, perhaps financial, or in terms of professional or international status, in the successful implementation of their idea." [18] Some attempt should be made to distinguish between, and compare results from, those trials carried out by those

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previously unattached to the treatments being assessed, and those whose careers have been focused upon the development of the involved treatments.

After the FINE trial released results in the manner laid out in its protocol and reported a null result, its sister trial PACE [8] published and interpreted results in ways which seriously deviated from its own protocol [13]. The abandonment of the 'positive outcome' criteria, a primary outcome, served to make it far easier for researchers to claim the treatments assessed were of clinical value, but the area where there has been the most concern has been related to claims about 'recovery' - clearly an emotional matter for patients who are so desperate to get better, but also have to endure the sort of prejudices seen above.

The PACE trial's published protocol [13] defined 'recovery' as requiring an SF-36 Physical Functioning (SF36-PF) questionnaire score of at least 85 out of 100, while the trial's entry criteria required a score of 65 or under, which was taken to indicate that patients' fatigue was disabling. The post-hoc criteria for recovery allowed patients with an SF36-PF score of 60 to be classed as recovered. This change was justified by the claim that a threshold of 85 would mean "approximately half the general working age population would fall outside the normal range." [19] In fact, the data cited showed that the median score for the working age population was 100, less than 18% of the general working age population had a score under 85, and 15% had declared a long-term health problem [20,21].

An SF36-PF score of 60 was claimed in the Lancet PACE paper to be the mean -1sd of the working age population, and thus a suitable threshold for 'normal' disability [8]. They had in fact used data which included all those aged over 65, reducing the mean physical function score and increasing the SD [20]. For the working age population the mean -1sd was over 70, requiring patients to score at least 75 to fall within this 'normal range' [21]. Also, the trial's protocol makes it clear that the thresholds for recovery (including ≥ 85 for SF-36 PF) were intended to be more demanding than those for the mean -1sd, reporting that: "A score of 70 is about one standard deviation below the mean... for the UK adult population" [13]. Patients could be classed as recovered when reporting no change, or even a decline, in either of the trial's primary outcomes.

Even using the loose post-hoc criteria for recovery, only 22% of patients were classed as recovered following treatment with specialist medical care and additional CBT or GET [19]. Regardless, the BMJ had reported that PACE showed CBT and GET "cured" 30% and 28% of patients respectively [22], a Lancet commentary which had been reviewed by the PACE trial's researchers claimed that about 30% recovered using a "strict criterion" for recovery [23], and a paper aimed at NHS commissioners stated PACE indicated a recovery rate of 30-40% for CBT and GET [24,25]. It is not surprising that such misstatements of fact will cause problems for patients, promote unwarranted assumptions and prejudices, and lead to a culture of distrust.

While patient's expectations for treatments were recorded before treatments in PACE began, and this showed greater expected gain for APT than CBT and GET, this should not reassure us that improvements in self-reported outcome measures were not a result of bias. The therapists and participants manuals for CBT and GET all include positive claims about the efficacy of the treatment being assessed which would be likely to affect patient's expectations, and equivalent claims were not made to those receiving APT, eg: "In previous research studies, most people with CFS/ME felt either 'much better' or 'very much better' with GET." [GET participant manual, p28] [26] More generally, there should be concern that any biopsychosocial intervention intending to alter patient cognitions or understanding of themselves is likely to lead to problems with bias on self-report measures. The description of CBT used in the 2001 Lancet study [4] makes it clear that challenging the patient's view of themselves as a patient is a core part of the intervention [27]. Any analysis of outcome data should be done with an awareness of the danger that patients may then try to describe their health more positively, despite not having seen any real improvement in health.

Considering the problems detailed above, and your own criteria, it is surprising that the PACE trial was classed as being of good quality.

Unfortunately, I do not think that I have time to properly raise important matters about the social context in which biopsychosocial approaches need to be assessed (I know that you wanted another five pages of this). In the draft report's assessment of potential harms related to diagnosis, I do not think that this was done well, and seemed to slip into presenting the harms of illness as being overly related to diagnosis, as well as failing to think seriously about why certain unreasonable prejudices can affect medical staff and harm patients. I think that the above example from the FINE trial, and wider concerns about the exaggerated claims made for the benefits of biopsychosocial approaches should be considered. Also - surely you can just use your imagination and recognise: "Chronic Fatigue Syndrome: if you're seriously disabled with that people are going to make fun of you". It's difficult to imagine anyone coming up with a name like that, or 'chronic multisymptom illness' or 'feel too poorly disease' without realising that it will lead to patients facing derision.

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One important point relating to the harms of diagnosis, is the potential financial cost of a diagnosis of CFS over ME. In a talk Peter White gave to Swiss Re Insurers he explained that a diagnosis of CFS can fall under an insurance policies mental health exclusion: "The point made is that a diagnosis of Myalgic Encephalomyelitis or ME (a term often used colloquially instead of CFS) is considered a neurological condition according to the arrangement of the International Classification of Diseases (ICD) diagnostic codes whereas CFS can alternatively be defined as neurasthenia which is in the mental health chapter of ICD10." [28] Some important stakeholders have a clear interest in ME/CFS patients being given a diagnosis which allows them to be classed as mentally ill, or that their ill health is a result of a refusal to think and behave as they should. The PACE trial's three Primary Investigators all reported conflicts of interest involving the insurance industry. [8]

There has also been considerable concern from a range of disability campaigners about the way the biopsychosocial model has been used by the insurance industry and UK government to undermine the interests of the sick and disabled [29-33]. Allowing a group of researchers and medical staff to claim authority over how patients diagnosed with a condition like ME/CFS should think and behave has clear political and moral implications, and too often, matters in this area are decided within processes that give little real power to patients themselves.

While not overflowing with praise for the research around ME/CFS, I still do not believe that the draft report was sufficiently critical, or that you have been able to take the time to do the reading and thinking necessary to write a worthwhile report on this difficult topic. I am concerned that this process is being rushed, and that more time and involvement from patients will be needed in order to avoid this being another semi-thought out piece of work that serves to make life worse for patients. Trying to apply similar methods to writing a report on ME/CFS that one would use for a condition that could be reliably diagnosed, and for which treatments could be either objectively assessed or tested under blinded conditions, is not going to work. This report will need to make important moral and political judgments in complicated and uncertain areas, and cannot pretend that the peer reviewed literature in this area already includes the most important thoughts and opinions - attempting to do so will lead to yet more problems.

- [1] <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1371151/>
- [2] <http://www.amjmed.com/article/0002-9343%2893%2990183-P/abstract>
- [3] <http://www.amjmed.com/article/S0002-9343%2899%2980332-5/abstract>
- [4] <http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2800%2904198-2/abstract>
- [5] <http://www.ncbi.nlm.nih.gov/pubmed/15585538>
- [6] <http://www.ncbi.nlm.nih.gov/pubmed/18827302>
- [7] <http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=7826378&fileId=S0033291709992212>
- [8] <http://www.ncbi.nlm.nih.gov/pubmed/21334061>
- [9] <http://www.biomedcentral.com/1471-2377/7/6/comments#306608>
- [10] <http://www.ncbi.nlm.nih.gov/pubmed/17369597>
- [11] <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0040808>
- [12] <http://qjmed.oxfordjournals.org/content/early/2013/03/28/qjmed.hct061.full>
- [13] <http://www.biomedcentral.com/1471-2377/7/6>
- [14] <http://www.bmj.com/content/340/bmj.c1777>
- [15] <http://www.fine-trial.net/downloads/CFS%20patient%20presentation.pdf>
- [16] <http://www.ncbi.nlm.nih.gov/pubmed/22192566>
- [17] <http://psychologyatmanchester.edublogs.org/2013/08/02/interview-with-prof-alison-wearden-by-as-level-work-experience-students/>
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- [22] <http://www.bmj.com/content/342/bmj.d1168>
- [23] http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2811%2960172-4/fulltext#article_upsell
- [24] <http://www.biomedcentral.com/1472-6963/11/217>
- [25] <http://www.thenakedscientists.com/HTML/content/news-archive/news/2384/>
- [26] <http://www.pacetrail.org/trialinfo/>
- [27] Bleijenberg G, Prins J, and Bazelmans E. 'CHAPTER 23: Cognitive-Behavioral Therapies' in 'Handbook of Chronic Fatigue Syndrome' 2003; John Wiley & Sons
- [28] http://www.swissre.com/clients/newsletters/Managing_claims_for_chronic_fatigue_the_active_way.html
- [29] <http://www.theguardian.com/commentisfree/2008/mar/17/epluribusunum>

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- [30] <http://disability-studies.leeds.ac.uk/files/library/A-Tale-of-two-Models-Leeds1.pdf>
- [31] http://www.midmoors.co.uk/Unum/unum_in_uk.pdf
- [32] <http://internationalgreensocialist.wordpress.com/illness-as-deviance-work-as-glittering-salvation-and-the-psyching-up-of-the-medical-model-strategies-for-getting-the-sick-back-to-work/>
- [33] <http://dpac.uk.net/2014/09/gordon-waddells-biopsychosocial-attack-on-disabled-people/>

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October 20, 2014

The Solve ME/CFS Initiative and our Research Advisory Council thank the Evidence-Based Practice Center and AHRQ for preparing this report and for the attention to detail in the comprehensive review of the literature. Below we have provided specific areas of comment and correction in the suggested format for the authors to consider as they finalize this document.

Structured Abstract

On page vi of the conclusions in the structured abstract, either list all interventions that showed benefit or state simply that there are several interventions that showed benefit. The conclusions should not list only CBT and GET as beneficial.

Introduction

On page 2, last sentence of 1st paragraph, *“Economic impact is considerable with most adult patients never*

returning to work.”^{9,21} the original economic impact papers (there are 3) should be cited rather than these review articles

On page 1, 3rd paragraph of the Introduction, it indicates that few if any risk factors have been identified. However, there are several published epidemiology, birth cohort, twin and primary care studies that have identified risk markers including being female, recent viral infection, genetic vulnerability and family history. All of these provide important and potential diagnostic clues for ME/CFS and while excluded from the review, should at least be noted in the Introduction.

On page 1 of the Introduction it is stated, *“This review is not intended to address the question of etiology nor underlying factors that lead to the onset or perpetuation of ME/CFS but rather to focus on the diagnosis and treatment of this syndrome.”*

- It would be helpful to clarify how diagnosis is possible without understanding the cause or perpetuating factors of ME/CFS. We believe what is intended here is to help the reader understand that the review will focus on evidence using symptoms for diagnosis versus objective markers (since none have been validated) or possible causes (since no causal factors have been confirmed).

The last sentence of the Introduction on page 2, *“This report is not intended to be used or likely to be useful to develop criteria for disability or insurance”* somewhat contradicts what is stated on page ii, *“The final report (not draft) may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies”* and should be clarified/corrected.

Methods

In the Literature Search Strategy on page 4 it is noted that *“scientific information packets were requested from drug and device manufacturer who potentially had data on the use of medications or devices for ME or CFS, who had the opportunity to submit data using the portal for submitting scientific information packets on the Effective Health Care Program Web site. Seventeen submissions were received”*. However, it is not clear where these 17 submissions are listed, how they were analyzed, included or excluded and whether they provided evidence-based information.

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Results

Incorrect citation for the study at the bottom of page 19, “*Specifically, 21 patients had been given a psychiatric diagnosis when one did not exist, and 13 patients who had never been given a psychiatric diagnosis actually had a treatable psychiatric condition in addition to CFS.*”⁵² Please note we do not know what the correct citation is, only that citation 52 is not correct.

On page 22 under Medications, even though rintatolimod is not FDA approved, at one time it was approved (and it still may be approved) for compassionate use. If this is true, this should be added to this section.

Discussion

The authors should add a paragraph describing the strengths and limitations of comparative effectiveness systematic reviews for medically unexplained disorders like ME/CFS where comparative little to no comparative effectiveness has been conducted.

General Comment

Even though the review points out the lack of coherence in the field and the absence of high quality clinical trial data, this systematic review would be greatly improved and the field would benefit from an acknowledgement and citation of the substantial body of etiology and biomarker research that can in fact provide clues to diagnostic criteria and potential identification of ME/CFS subtypes. For example, all of the studies that attempted to objectively assess the autonomic nervous system and sleep disturbances (using polysomnography for example) were excluded from this review and not used to address Key Question 1. The same is true for the many important endocrine, neurology and immune studies that have been conducted in an attempt to identify subtypes as well as understand pathophysiology. While these studies may not meet comparative effectiveness review criteria, they are important steps and do provide important clues that could be used to model ME/CFS and inform further fruitful areas of study – including the identification of diagnostic criteria. This seems to be the “Catch 22” for ME/CFS; little funding resulting in small studies of heterogeneous populations. Even still, biological signals do appear to be

emerging from some of the clinical trials that were directed at possible etiology (e.g., rintatolimod) and biomarkers such as heart rate variability.

Comments on aspects of AHRQ's systematic review of the Diagnosis and Treatment of Myalgic

Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

PD White¹, T Chalder², R Moss-Morris³, M Sharpe⁴, AJ Wearden⁵

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Harms associated with graded exercise therapy

The abstract states: "Although adverse effects were not well reported across trials, GET compared with CBT or control groups was associated with a higher number of reported adverse events and withdrawal rates in several trials", and in the conclusions – "GET appears to be associated with harms in some patients..." The first statement seems to imply that adverse effects of a treatment are the same as adverse events that occur when receiving a treatment, when this is not the case. Adverse "effects" are caused by a treatment, which is why they are more commonly called adverse "reactions", whereas adverse events are not necessarily related to a treatment and may be more related to the natural course of the illness or a comorbid illness. We note that the current draft confuses adverse events with harms due to treatment throughout the document.

ES-28 "The harms associated with exercise were generally more implied than specifically stated in the exercise trials.67-70 In the combination trials, the greatest number of harms were in the GET arm of one trial, 69 lowest adherence was in the exercise arm in another trial, 68 and several trials had greatest withdrawal due to adverse events in the exercise arms.67,70"

We suggest that there are a number of errors in these statements, which we detail below. ES-12 and Page 21 "... patients receiving GET reported more adverse effects compared with CBT, adaptive pacing, or usual care in one good-quality trial.."

This statement referring to the PACE trial (www.pacetrial.org), of which some of us we were the principal investigators, is a misinterpretation of the trial results, and does not take into account statistical significance. The safety data from this trial were given in table 4 of White et al, 2011, which shows the results of six different adverse outcomes across the four arms of the trial. Most importantly there were very few serious adverse reactions to treatment (i.e. adverse treatment effects), with no statistical difference across treatment arms.

Although there were more serious adverse events (SAEs) in GET compared to CBT and specialist medical care alone (SMC), there was a similar number in the adaptive pacing therapy (APT) arm, and, of course, SAEs were judged to be independent of treatment by independent scrutineers. Therefore it would be inaccurate to interpret SAEs as evidence of harm relating to treatment. Similarly there were no statistically significant differences in the proportions suffering from serious deterioration. In particular there were no differences in withdrawals from treatment due to worsening across treatment arms (this result needs to be incorporated into the table on ES-23 and ES-22).

We examined non-serious adverse events (NSAEs) and other safety measures in the PACE trial in more detail in Dougall et al, 2014. The number of NSAEs did not differ between

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treatment arms either when considered as a whole (table 1) or when only considering NSAEs attributed to CFS (table 2). Table 5 in this paper shows there were no differences across the four treatment groups in the proportion of patients reporting deterioration in fatigue (one of the primary outcomes) after treatment. On the second primary outcome, physical function,, a significantly greater proportion of patients showed deterioration after APT (25%) and r SMC (18%) than after CBT (9%) or GET (11%)(table 5).

Page 21 "...and almost half of patients assigned to physiological exercise testing (10/25) refused to repeat testing at follow-up over concern for harm."

This refers to Moss-Morris 2005, but the physiological exercise testing was an outcome measure, not part of GET. You do not mention that 12/24 participants in the control arm also declined exercise testing, compared to 11/25 participants receiving GET (Table 4). Only 3 participants dropped out after GET compared to 3 in the control arm. We think you should consider revising your interpretation of these data as evidence of harm of GET.

ES-12 "...and there were more withdrawals in the GET group in several trials."

This is not the case. There have been 6 RCTs of GET for CFS published (Fulcher, Powell, Wearden, Moss-Morris, Wallman, White), although there are published trials of other exercise interventions. The proportions withdrawing from GET versus the control arm were similar in all but one trial (Wearden et al, 1998). The proportions of participants withdrawing from GET in the largest (PACE) trial were the smallest (6%) compared to all other treatment arms (7, 9, and 11%), although differences were not significant (White et al, 2011; table 2). Wearden's (1998) trial intervention was designed as a fitness training intervention rather than graded exercise therapy. The intervention had higher starting levels of exercise intensity than the other trials, and exercise progression was based on change in heart rate, which probably explains the higher drop-out rates (Wearden et al, 1998).

ES-28 "Several previous studies have found worsening effects with exercise and a survey sponsored by the ME Association found that patients believed that GET made more people worse compared with other treatments.71,72"

The problem with generalising from surveys of patient organisations are two-fold: 1) We do not know what the survey members' diagnoses were, and we are aware of one study showing high rates of non-CFS diagnoses in such a patient organisation. Brimmer and colleagues (2013) found that 59% of 49 US patient support group members had an exclusionary condition, and only 35% met criteria for CFS. 2) We do not know if they really did receive graded exercise therapy; one qualitative study of such a survey found significant variation in content and delivery of treatment received (Gladwell et al, 2014). Since the randomised controlled trials do not generally suggest that harm follows GET, we suggest that caution is necessary before generalising from such surveys.

References

Brimmer, D. J., Maloney, E., Devlin, R., Jones, J. F., Boneva, R., Nagler, C. & Unger, E. R. (2013). A pilot registry of unexplained fatiguing illnesses and chronic fatigue syndrome. *BMC research notes*,2013; 6(1): 1-11.

Dougall D, Johnson AL, Goldsmith K, Sharpe M, Angus B, Chalder T, White PD. Adverse events and deterioration reported by participants in the PACE trial of therapies for chronic fatigue syndrome. *Journal of Psychosomatic Research* 2014; 77: 20-26.

Fulcher KY, White PD. Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. *BMJ* 1997; 314: 1647-52.

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Gladwell PW, Pheby D, Rodriguez T, Poland F. Use of an online survey to explore positive and negative outcomes of rehabilitation for people with CFS/ME. *Disability and Rehabilitation* 2014; 36: 387-394.

Moss-Morris R, Sharon C, Tobin R, Baldi JC. A randomized controlled graded exercise trial for chronic fatigue syndrome: outcomes and mechanisms of change. *J Health Psychol* 2005; 10: 245–59.

Powell, P., Bentall, R. P., Nye, F. J., & Edwards, R. H. T. (2001). Randomized controlled trial of patient education to encourage exercise in chronic fatigue syndrome. *BMJ* 2001; 322, 1–5.

Wallman, K. E., Morton, A. R., Goodman, C., Grove, R., & Guilfoyle, A. M. Randomised controlled trial of graded exercise in chronic fatigue syndrome. *The Medical Journal of Australia*, 004; 180, 444–448.2

Wearden AJ, Morriss RK, Mullis R et al. Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. *Br J Psychiatry* 1998; 172: 485–90.

White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, Baber HL, Burgess M, Clark LV, Cox DL, Bavinton J, Angus BJ, Murphy G, Murphy M, O’Dowd H, Wilks D, McCrone P, Chalder T, Sharpe M, and on behalf of the PACE trial management group. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *The Lancet* 2011;377:823-36.

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Date: October 19, 2014

To: Scientific Resource Center
Portland VA Research Foundation

Subject: AHRQ Evidence Review for the Diagnosis and Treatment of
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Over the past three decades, the disease known by the World Health Organization as “Myalgic Encephalomyelitis” has been misrepresented and distorted by those who lack a true understanding of the nature of the disease. The creation of overly broad definitions and a new name has only served to further obfuscate the situation.

The draft AHRQ Evidence Review currently states “*Multiple case definitions have been used to define ME/CFS and those that require the symptoms of post-exertional malaise and neurological and autonomic manifestations appear to represent a more severe subset of the broader ME/CFS population.*”³ However, it is the decided opinion of ME/CFS experts, clinicians, patients and advocates that the ***symptoms of post-exertional malaise and neurological and autonomic manifestations represent ALL patients with the disease being measured.*** Patients who do not have these symptoms do NOT have the disease in question.

It is my understanding that a vital Key Question was omitted as a workshop goal due to a lack of research: “*Do the set of ME/CFS definitions encompass the same disease, a spectrum of diseases, or separate discrete conditions and diseases that do not belong together?*” Respectfully, failure to separate this disease from other fatiguing illnesses (misidentified as “the broader ME/CFS population” in this draft) is a fatal flaw in this process.

As you are likely aware, the Institute of Medicine is reviewing the issue of diagnostic criteria at this very moment. ***The National Institutes of Health and the AHRQ would be wise to delay a final report and the P2P workshop meeting until that study has been published.*** Unless and until that very basic question can be answered, the results of this workshop will be of little or no practical use.

¹ The Structured Abstract (Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS))

³ The Structured Abstract (Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS))

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October 20, 2014

Dear Dr. Collins,

I would like to object to the idea that works suggesting that cognitive behavioral therapy (CBT) and graded exercise therapy (GET) are relevant to the understanding of the disease that the NIH is now choosing to call "ME/CFS."

A critique of the most prominent of these studies follows. Other CBT/GET studies are characterized by these same flaws.

In addition, a list of research studies looking at the physiological abnormalities that have been found in studies of patients qualifying for CFS or ME diagnoses follows. I request that these studies all be considered in any literature reviews that the NIH may conduct.

In particular, this study is about the Lake Tahoe cohort, was published in a prestigious journal and was authored by respected researchers. I therefore request that it not be overlooked in the consideration of this disease.

Buchwald D, Cheney PR, Peterson DL, Henry B, Wormsley SB, Geiger A, Ablashi DV, Salahuddin SZ, Saxinger C, Biddle R, et al. A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpesvirus type 6 infection. *Ann Intern Med.* 1992 Jan 15;116(2):103-13. PMID: 1309285

Cordially,

Lisa Petrison, Ph.D.
Executive Director
Paradigm Change
www.paradigmchange.me

PROBLEMS WITH THE PACE STUDY: A BRIEF CRITIQUE

By Lisa Petrison, Ph.D.

THE STUDY:

White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, Baber HL, Burgess M, Clark LV, Cox DL, Bavinton J, Angus BJ, Murphy G, Murphy M, O'Dowd H, Wilks D, McCrone P, Chalder T, Sharpe M; PACE trial management group. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome

(PACE): a randomised trial. Lancet. 2011 Mar 5;377(9768):823-36.
PMID: 21334061

[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(11\)60096-2/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext)

www.pacetrial.org/trialinfo.html

<http://www.meactionuk.org.uk/FULL-Protocol-SEARCHABLE-version.pdf>

STUDY BACKGROUND:

This study was conducted by a team of psychiatrists in the UK between 2005 and 2010. It cost a total of 5 million pounds (\$8 million), and was funded by the UK Medical Research Council, the Department of Health for England, the Scottish Chief Scientist Office, and the Department for Work and Pensions.

Participants consisted of 641 individuals meeting the Oxford criteria for chronic fatigue syndrome (with fatigue as the only symptom, accompanied by significant disability in the absence of an exclusionary medical or psychiatric diagnosis). All subjects were age 18 or over, and they had to be well enough to be able to attend 14 or more sessions of therapy over a 52 week period.

All patients received a lecture and a pamphlet from a medical practitioner specializing in the disease. They then were divided into four groups.

Patients in the “cognitive-behavioral therapy” (CBT) condition discussed with therapists ways in which they might arrange their lives so that they could participate in a modest amount of activity and exercise each day. A goal was to have the amount of exercise very gradually increase over time. Topics discussed in the sessions included the importance of planning out each day’s activities in advance and sticking to that schedule as well as ways to reduce general stressors in life.

Patients in the “graded exercise therapy” (GET) condition also were encouraged to engage in modest amounts of exercise each day, and were taught how to use a heart rate monitor to make sure that they did not exceed their limitations. Again, a goal was to have the amount of

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exercise gradually increase over time. Patients were encouraged to engage in physical routines thought to be conducive to physical conditioning, such as doing extensive stretching before exercising.

Patients in the “adaptive pacing therapy” (APT) condition worked with therapists to monitor their condition, to make sure that they were not doing more than their bodies would allow. Their goal was to conserve energy to the extent that they were able.

Patients in the control condition received no treatment other than the lecture and pamphlet from the medical practitioner.

After 52 weeks, patients were evaluated on a number of dimensions.

The “Chalder Fatigue Scale” had patients rate their own current level of fatigue. Patients in the CBT and GET groups rated their fatigue as significantly (about 15%) lower on average than those in the APT and control groups.

The “Physical Functioning” scale had patients rate their ability to engage in a variety of activities (such as walking or climbing stairs). Patients in the CBT and GET groups rated their ability as significantly (about 10%) higher on average than those in the APT and control groups.

A “Six Minute Walking Test” gauged how far patients could walk in six minutes. The patients in the GET group were able to walk significantly (a

little less than 10%) further on average than patients in the other three groups.

Based on this, GET and CBT were deemed by the authors to be successful treatments for CFS. These therapies are currently are incorporated into the NICE (National Institute for Health and Clinical Excellence) Guidelines as the only accepted treatments for the disease in the UK, and received a substantial amount of favorable media coverage in both the US and UK.

STUDY CRITICISMS:

Following is a critique of methodological problems with this study.

Effect Sizes:

One problem is that although the large sample size meant that the findings achieved statistical significance, the actual effect sizes were quite small.

At the beginning of the study, subjects scored an average of about 27 on the 33-point Chalder Fatigue Scale (described below). By the end of the 52 weeks, patients in all the groups improved. Those in the control condition scored 24, compared to 20 in the CBT condition and 21 in the GET condition. While this was a significant difference, the magnitude of difference between groups was small. On average, patients in all the groups stated that they continued to be more fatigued than before they got sick on the equivalent of every item on the scale.

At the beginning of the study, subjects scored about 38 on the 100-point Physical Functioning scale (also described below). By the end of the 52 weeks, patients in all three groups improved. Those in the control group scored an average of 51, compared to an average of 58 in both the CBT and GET groups. On average, patients in all groups remained limited in their ability to do basic activities such as carry groceries, walk up a flight of stairs or bathe themselves.

For the six-minute walking test, patients in the GET condition were able to walk an average of 379 meters (compared to 312 at the beginning of the study). This was a significantly bigger improvement than that of the control

group, who could walk an average of 348 meters (compared to 326 at the beginning of the study). However, it was still substantially less than the distance (631 meters) that healthy people aged 65+ were able to walk in six minutes in another study (Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J* 1999; 14: 270-274, PMID: 10515400).

Appropriateness of Dependent Variables:

CFS is a multisystemic illness with a wide variety of symptoms other than fatigue. The authors failed to incorporate that fact into their

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study. The reported effects centered on only three variables -- fatigue, physical functioning and (for the GET condition) six-minute walking ability.

Cognitive functioning (a key issue in the disease) was measured and did not differ significantly across groups at the end of the 52 weeks. Problems with other types of symptoms or functioning issues were not measured.

The Chalder Fatigue Scale and Physical Functioning Scale are both subjective measurements. Conceivably, patients who had received 14 sessions of therapy may have been more inclined to report improvements than those who had received no therapy -- even if that wasn't reflective of reality -- because they had the underlying desire to feel their time wasn't wasted or to make it seem like the therapist had been helpful.

The one objective measurement showing an effect -- the six-minute walking test -- is not reflective of patients' lives as a whole. By definition, CFS patients' abilities are constrained less by their inability to participate in activity than by the negative effects that they experience afterwards.

For instance, one study on exercise by another group demonstrated (by having patients wear a device to track all their movements throughout the day) that patients who participated in structured exercise reduced their activity at other times to compensate. (Black CD, McCully KK. Time course of exercise induced alterations in daily activity in chronic fatigue syndrome. *Dyn Med*. 2005 Oct 28;4:10. PMID: 16255779) Conceivably, patients in the GET condition might have pushed themselves to walk fast for six minutes to demonstrate their success in the program, then spent the next day or week in bed.

Study Population:

Another group of criticisms is related to the patient population who participated in the study.

Patients had to be able to attend 14 or more sessions at a hospital clinic. Thus, those who were severely ill with CFS (housebound or

bedbound) were excluded. Whether any of the study findings might be applicable to them is wholly unknown.

The use of the Oxford definition -- which uses no symptoms other than fatigue in the criteria -- presents another problem. Fatigue is just one of many symptoms in CFS, and it is characteristic of many other illnesses as well. In particular, it is a symptom of major depression, and the PACE study did not exclude people who were depressed.

The authors reported that some of the people in the study indeed had plain depression rather than CFS. Since people with depression are known to benefit from psychotherapy and exercise, the inclusion of even a few of these individuals could have skewed the results enough to make it look like the interventions were helpful for subjects in general, even if they were of no help to any patients with CFS.

As a result of criticisms of the study population, the authors re-ran the data to determine if there were interaction effects between a) those patients who met the CDC (Fukuda) criteria for CFS vs. those who did not and b) the experimental condition (GET, CBT, APT or control). The dependent variables were the Chalder Fatigue Scale and the Physical Function Scale. They found no such interactions.

However, not finding an interaction does not mean that there is no actual underlying interaction, since it may be that insufficient sample size was responsible for the lack of significant effect. If the authors wanted to show that people meeting the CDC criteria improved more in the GET or CBT conditions than in the control condition, they should have done an analysis of main effects just on those people. The fact that they did not report this in the paper suggests that they did not have enough people who met the CDC criteria to prove that the small effect sizes were not due to chance.

The CDC definition of CFS is itself quite broad. For instance, people who do not have post-exertional exhaustion (the recognized cardinal symptom of the illness) can qualify. Especially since the authors' results and hypotheses were counter to more than 50 studies in the medical literature showing various negative physiological effects as a result of exercise in CFS patients, the use of a more restrictive definition would have been appropriate.

Study Implementation:

The write-up of the study made it seem that any improvements that occurred were due to increased exercise as a result of physical therapy or psychotherapy. The instructions given to therapists suggest that this may not have been the case, however.

For one thing, subjects in the groups receiving therapy were given counseling that may have helped their condition in ways unrelated to exercise. In the CBT condition, people were encouraged to find ways to reduce stress in their lives -- conceivably allowing them to need to push themselves less hard and thus to experience physical improvements as a result of increased rest. In the GET condition, sleep hygiene skills (such as taking a hot bath before bedtime) were discussed. Since sleep is disordered in CFS, this may have helped their physical condition.

Therapists were instructed to remain sympathetic and supportive of the patients. In general, people who are having a difficult time often benefit psychologically from any sort of positive attention, perhaps especially from therapists. It could be that people who were getting GET or CBT felt emotionally better as a result of the interactions and that this affected their perceptions (but not the reality) of how they were doing physically.

Subjects in both the GET and CBT conditions were encouraged to start out with very gentle exercise (relying either on a heart rate monitor or on their physical responses) and to increase the amount very gradually. On the other hand, newly diagnosed CFS patients who are not receiving coaching tend to engage in a push/crash phenomenon -- exercising vigorously and then experiencing extended post-exertional exhaustion. Conceivably, patients in the GET and CBT conditions actually might have been exercising less on average than patients in the control condition, with their increased energy

and improved physical function resulting from having pushed themselves less hard throughout the year.

Another issue concerns the possibility that GET and CBT are often not implemented by other therapists in the ways that they were in the study. Therapists in this study were instructed to be particularly supportive and received in-depth training in the particular

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methodologies used -- for instance, with strong emphasis placed on the idea of extremely gradual increases in activity. Therapists who are less focused on clients' individual situations and who push hard for faster improvements might generate very different results.

In addition, the 14 sessions of therapy that patients received may be unrealistic in the real world, considering restraints on healthcare spending. Fewer sessions might not provide the same results.

Reporting:

Especially when describing the study to the media, the authors and others promoting it frequently have made the results sound more impressive than they actually are. None of the groups of patients achieved a recovery to anything even close to normal levels of functioning, and the magnitude of differences between getting extensive treatment vs. no treatment were very small.

These researchers and their supporters repeatedly have made statements listing the percentage of subjects in the GET and CBT conditions who have improved, without stating the percentage in the control condition who improved.

For instance, for the Physical Function Scale, about 70% of patients in the GET and CBT conditions improved, compared to 58% in the control condition. For the Chalder Fatigue Scale, 76-80% of patients in the CBT and GET conditions improved, compared to 65% in the control condition. For participant ratings of subjective overall global health, 41% of those in the GET and CBT conditions improved, compared to 25% of those in the control condition.

Statements such as "41% of patients receiving GET and CBT improved" thus are misleading, since the majority of those individuals would have improved without any treatment at all.

Contrast with Findings in Medical Literature

More than 50 papers on exercise intolerance in CFS patients have been published by medical researchers. These papers demonstrate a wide variety of abnormal negative physiological changes in patients, usually lasting for days (sometimes longer) after the exercise occurs.

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The authors of the PACE study state that they are operating under the theory that the problems that patients have with exercise is that they are deconditioned or have an irrational fear of exercise. This is not consistent with the peer-reviewed medical literature, which shows changes related to a wide variety of physiological measures (such as inflammation and oxidative stress) that have nothing to do with muscle conditioning or exercise phobia. The authors' hypothesis also is not consistent with the observed experience of the illness, in which many extremely fit individuals become permanently bedridden overnight.

Chalder Fatigue

Scale: 33 points

possible

1. Do you have problems with tiredness?
2. Do you need to rest more?
3. Do you feel sleepy or drowsy?
4. Do you have problems starting things?
5. Do you lack energy?
6. Do you have less strength in your muscles?
7. Do you feel weak?
8. Do you have difficulty concentrating?
9. Do you make slips of the tongue when speaking?

10. Do you find it more difficult to find the correct word?
11. How is your memory?

Items 1-10: Less than usual, 0; No more than usual, 1; More than usual, 2; Much more than usual, 3.

Item 11: Better than usual, 0; No worse than usual, 1; Worse than usual, 2; Much worse than usual, 3.

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SF-36 Physical Function Sub-

scale: 100 points possible

The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

1. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports
2. Moderate activities such as moving a table, pushing a vacuum cleaner, bowling or playing golf
3. Lifting or carrying groceries
4. Climbing several flights of stairs
5. Climbing one flight of stairs
6. Bending, kneeling or stooping
7. Walking more than a mile
8. Walking several hundred yards
9. Walking one hundred yards
10. Bathing or dressing yourself

Scale: Not limited at all, 0; Yes, limited a little, 5; Yes, limited a lot, 10.

ME/CFS and Medical Abnormalities Medical Research

CFS Overview:

Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles AP, Speight N, Vallings R, Bateman L, Baumgarten-Austrheim B, Bell DS, Carlo-Stella N, Chia J, Darragh A, Jo D, Lewis D, Light AR, Marshall-Gradisbik S, Mena I, Mikovits JA, Miwa K, Murovska M, Pall ML, Stevens S. Myalgic Encephalomyelitis: International Consensus Criteria. *J Intern Med.* 2011 Jul 20. PMID: 21777306

In view of recent research and clinical experience with CFS that strongly point to widespread inflammation and multisystemic neuropathology, it is more appropriate and correct to use the term "myalgic encephalomyelitis"(ME), because it indicates an underlying pathophysiology. Consequently, an International Consensus Panel consisting of clinicians, researchers, teaching faculty and an independent patient advocate was formed with the purpose of developing criteria based on current knowledge. Clinical and research application guidelines promote optimal recognition of ME by primary physicians and other health care providers, improve consistency of diagnoses in adult and paediatric patients internationally, and facilitate clearer identification of patients for research studies.

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Bansal AS, Bradley AS, Bishop KN, Kiani-Alikhan S, Ford B. Chronic fatigue syndrome, the immune system and viral infection. *Brain Behav Immun*. 2011 Jul 2. PMID: 21756995

The authors review what is known about the immune system in CFS. Slightly increased parameters of inflammation and pro-inflammatory cytokines such as interleukin (IL) 1, IL6 and tumour necrosis factor (TNF) α are likely present. Additionally, impaired natural killer cell function appears evident. Alterations in T cell numbers have been described by some and not others. While the prevalence of positive serology for the common herpes viruses appears no different from healthy controls, there is some evidence of viral persistence and inadequate containment of viral replication. The ability of certain herpes viruses to impair the development of T cell memory may explain this viral persistence and the continuation of symptoms.

*

May M, Emond A, Crawley E. Phenotypes of chronic fatigue syndrome in children and young people. *Arch Dis Child*. 2010 Apr;95(4):245-9. PMID: 19843509

Exploratory factor analysis was performed on symptoms present at assessment in 333 children and young people with CFS/ME. Three phenotypes were identified using factor

analysis: Factor 1, musculoskeletal, had loadings on muscle and joint pain and hypersensitivity to touch, and was associated with worse fatigue, physical function and pain. Factor 2, migraine, loaded on noise and light hypersensitivity, headaches, nausea, abdominal pain and dizziness and was most strongly associated with physical function and pain. Factor 3, sore throat, had loadings on sore throat and tender lymph nodes and was not associated with fatigue or pain.

*

Carlo-Stella N, Cuccia M. Demographic and clinical aspects of an Italian patient population with chronic fatigue syndrome. *Reumatismo*. 2009 Oct-Dec;61(4):285-9. PMID: 20143004

Besides persistent fatigue, a clinical syndrome of CFS with infectious, neurological and rheumatological characteristics is outlined from the data in Italy.

*

Bassi N, Amital D, Amital H, Doria A, Shoenfeld Y. Chronic fatigue syndrome: characteristics and possible causes for its pathogenesis. *Isr Med Assoc J*. 2008 Jan;10(1):79-82. PMID: 18300582

Several mechanisms have been suggested to play a role in CFS, such as excessive oxidative stress following exertion, immune imbalance characterized by decreased natural killer cell and macrophage activity, immunoglobulin G subclass deficiencies (IgG1, IgG3) and decreased serum concentrations of complement component. Autoantibodies were also suggested as a possible factor in the pathogenesis of CFS. Recent studies indicate that anti-serotonin, anti-microtubule-associated protein 2 and anti-muscarinic cholinergic receptor 1 may play a role in the pathogenesis of CFS. It has been demonstrated that impairment in vasoactive neuropeptide metabolism may explain the symptoms of CFS.

*

Hooper M. Myalgic encephalomyelitis: a review with emphasis on key findings in biomedical research. *J Clin Pathol*. 2007 May;60(5):466-71. PMID: 16935967

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A review of research findings in CFS, termed a “chronic multiple-symptom, multiorgan, multisystem illness.”

*

Klimas NG, Koneru AO. Chronic fatigue syndrome: inflammation, immune function, and neuroendocrine interactions. *Curr Rheumatol Rep*. 2007 Dec;9(6):482-7. PMID: 18177602

Studies of CFS patients show a variety of dysfunctions, including mitochondrial dysfunction and immune dysfunction.

*

Miike T. Childhood chronic fatigue syndrome. *Nihon Rinsho*. 2007 Jun;65(6):1099-104. PMID: 17561704

For children and adolescents with CFS, four major symptoms are important: sleep disorders, easy fatigability, disturbed learning and memorization and immunological problems.

*

Kuratsune H. Overview of chronic fatigue syndrome focusing on prevalence and diagnostic criteria. *Nihon Rinsho*. 2007 Jun;65(6):983-90. PMID: 17561686

Recent studies reveal that CFS can be understood to be a special condition based on the abnormality of neuroendocrine-immunologic system caused by the psycho-social stress and some genetic components. Under these conditions, a reactivation of various kinds of herpes virus infections and/or chronic infections might occur as a result of immune dysfunction, causing the abnormal production of several cytokines. A distinctive feature of CFS is thought to be the secondary brain dysfunction caused by the abnormal production of several cytokines.

*

Janal MN, Ciccone DS, Natelson BH. Sub-typing CFS patients on the basis of 'minor' symptoms. *Biol Psychol*. 2006 Aug;73(2):124-31. PMID: 16473456

The authors did an analysis of a population of CFS patients and came up with musculoskeletal, infectious and neurological subtypes.

*

Gurbaxani BM, Jones JF, Goertzel BN, Maloney EM. Linear data mining the Wichita clinical matrix suggests sleep and allostatic load involvement in chronic fatigue syndrome. *Pharmacogenomics*. 2006 Apr;7(3):455-65. PMID: 16610955

The authors provide basic data about a group of CFS sufferers in Wichita, Kansas.

*

Jason LA, Taylor RR, Kennedy CL, Jordan K, Huang CF, Torres-Harding S, Song S, Johnson D. A factor analysis of chronic fatigue symptoms in a community-based sample. *Soc Psychiatry Psychiatr Epidemiol*. 2002 Apr;37(4):183-9. PMID: 12027245

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Individuals with chronic fatigue have symptoms that can be differentiated into theoretically distinct factors, including: Lack of Energy, Physical Exertion, Cognitive Functioning, and Fatigue and Rest.

Cancer Risk

Chang CM, Warren JL, Engels EA. Chronic fatigue syndrome and subsequent risk of cancer among elderly US adults. *Cancer*. 2012 Dec 1;118(23):5929-36. PMID: 22648858

CFS was associated with an increased risk of non-Hodgkin lymphoma (NHL). Among NHL subtypes, CFS was associated with diffuse large B cell lymphoma, marginal zone lymphoma, and B cell NHL not otherwise specified. CFS was also associated, although not after multiple comparison adjustment, with cancers of the pancreas, kidney, breast, and oral cavity and pharynx.

*

Levine PH, Fears TR, Cummings P, Hoover RN. Cancer and a fatiguing illness in Northern Nevada--a causal hypothesis. *Ann Epidemiol*. 1998 May;8(4):245-9. PMID: 9590603

The authors investigated the possibility that chronic fatigue syndrome (CFS) predisposes to cancer by comparing the cancer pattern in an area in northern Nevada, where an outbreak of a fatiguing illness, which included cases of CFS, was reported, to an area in southern Nevada, where no such illness was reported. Higher incidences of NHL and primary brain tumors were noted in the two northern Nevada counties (Washoe and Lyon) in 1986 and 1987 respectively, compared to the southern Nevada (Clark) county.

*

Levine PH, Atherton M, Fears T, Hoover R. An approach to studies of cancer subsequent to clusters of chronic fatigue syndrome: use of data from the Nevada State Cancer Registry. *Clin Infect Dis*. 1994 Jan;18 Suppl 1:S49-53. PMID: 8148453

The authors consider whether the decreased natural killer cell function in CFS clusters may be related to brain/CNS tumors and non-Hodgkin's lymphoma, finding a trend that merits future research.

*

Levine PH, Peterson D, McNamee FL, O'Brien K, Gridley G, Hagerty M, Brady J, Fears T, Atherton M, Hoover R. Does chronic fatigue syndrome predispose to non-Hodgkin's

lymphoma? *Cancer Res*. 1992 Oct 1;52(19 Suppl):5516s-5518s; discussion 5518s-5521s. PMID: 1394166

The authors examined the prevalence of non-Hodgkins lymphoma in epidemic areas for CFS.

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Cardiac Abnormalities

Miwa K. Cardiac dysfunction and orthostatic intolerance in patients with myalgic encephalomyelitis and a small left ventricle. *Heart Vessels*. 2014 Apr 16. PMID: 24736946

A small left ventricle heart size with a low cardiac output was common in ME patients, in whom orthostatic intolerance was extremely common. Cardiac dysfunction with a small heart appears to be related to the symptoms of ME.

*

Kossaify A, Kallab K. Neurocardiogenic syncope and associated conditions: insight into autonomic nervous system dysfunction. *Turk Kardiyol Dern Ars*. 2013 Jan;41(1):75-83. PMID: 23518945

CFS and other conditions with an association with neurocardiogenic syncope are discussed.

*

Wyller VB, Helland IB. Relationship between autonomic cardiovascular control, case definition, clinical symptoms, and functional disability in adolescent chronic fatigue syndrome: an exploratory study. *Biopsychosoc Med*. 2013 Feb 7;7(1):5. PMID: 23388153

This research study suggests that a) disability of CFS patients is not only related to fatigue but to other symptoms as well; b) altered cardiovascular autonomic control is associated with certain symptoms; c) The CDC criteria are poorly associated with disability, symptoms, and indices of altered autonomic nervous activity.

*

Frith J, Zalewski P, Klawe JJ, Pairman J, Bitner A, Tafil-Klawe M, Newton JL. Impaired blood pressure variability in chronic fatigue syndrome--a potential biomarker. *QJM*. 2012 Sep;105(9):831-8. PMID: 22670061

At rest, low frequency heart rate variability (sympathetic) was significantly increased in CFS compared to controls, while parasympathetic markers were significantly reduced.

Total diastolic blood pressure spectral power was increased across all domains, with a shift towards sympathetic and away from parasympathetic SBPV. On standing, overall systolic response was significantly reduced with reductions in both sympathetic and parasympathetic components.

*

Miwa K, Fujita M. Small Heart With Low Cardiac Output for Orthostatic Intolerance in Patients With Chronic Fatigue Syndrome. *Clin Cardiol*. 2011 Nov 28. PMID: 22120591

A small size of left ventricular with low cardiac output was noted in subjects with orthostatic intolerance, and especially in those patients also suffering from CFS. A small heart appears to be related to both cerebral and systemic hypoperfusion.

*

Hollingsworth KG, Hodgson T, Macgowan GA, Blamire AM, Newton JL. Impaired cardiac function in chronic fatigue syndrome measured using magnetic resonance cardiac tagging. *J Intern Med*. 2011 Jul 27. PMID:

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Patients with CFS have markedly reduced cardiac mass and blood pool volumes, particularly end-diastolic volume: this results in significant impairments in stroke volume and cardiac output compared to controls. The CFS group appeared to have a delay in the release of torsion.

*

Bjerregaard P, Nallapaneni H, Gussak I. Short QT interval in clinical practice. *J Electrocardiol.* 2010 Sep-Oct;43(5):390-5. PMID: 20667544

A shorter-than-usual QT interval has been reported in patients with Chronic Fatigue Syndrome.

*

Stewart JM. Chronic fatigue syndrome: comments on deconditioning, blood volume and resulting cardiac function. *Clin Sci (Lond).* 2009 Oct 19;118(2):121-3. PMID: 19534728

Reduced cardiac stroke volume and cardiac output was demonstrated in more severely afflicted patients with CFS, and this is primarily attributable to a measurable reduction in blood volume.

*

Hurwitz BE, Coryell VT, Parker M, Martin P, Laperriere A, Klimas NG, Sfakianakis GN, Bilsker MS. Chronic fatigue syndrome: illness severity, sedentary lifestyle, blood volume

and evidence of diminished cardiac function. *Clin Sci (Lond).* 2009 Oct 19;118(2):125-35. PMID: 19469714

This study indicates that lower cardiac volume levels, displayed primarily by subjects with severe CFS, were not linked to diminished cardiac contractility levels, but were probably a consequence of a co-morbid hypovolaemic condition.

*

Miwa K, Fujita M. Cardiovascular dysfunction with low cardiac output due to a small heart in patients with chronic fatigue syndrome. *Intern Med.* 2009;48(21):1849-54. PMID: 19881233

CFS patients have low cardiac output due to a small left ventricular chamber. Frequently reported cardiovascular symptoms (including shortness of breath, dyspnea on effort, rapid heartbeat, chest pain, fainting, orthostatic dizziness, coldness of feet and hypotension) may be results of this.

*

Miwa K, Fujita M. Cardiac function fluctuates during exacerbation and remission in young adults with chronic fatigue syndrome and "small heart". *J Cardiol.* 2009 Aug;54(1):29-35. PMID: 19632517

CFS patients had small left ventricular heart chambers and poor cardiac performance, and this was correlated with the severity of their symptoms.

*

Miwa K, Fujita M. Small heart syndrome in patients with chronic fatigue syndrome. *Clin Cardiol.* 2008 Jul;31(7):328-33. PMID: 18636530

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A high percentage of CFS patients have a small heart, and this leads to orthostatic dizziness, foot coldness, pitting edema and other symptoms.

*

Naschitz JE, Slobodin G, Sharif D, Fields M, Isseroff H, Sabo E, Rosner I. Electrocardiographic QT interval and cardiovascular reactivity in fibromyalgia differ from chronic fatigue syndrome. *Eur J Intern Med.* 2008 May;19(3):187-91. PMID: 18395162

CFS is associated with a short corrected electrocardiographic QT interval (QTc).

*

Naschitz J, Fields M, Isseroff H, Sharif D, Sabo E, Rosner I. Shortened QT interval: a distinctive feature of the dysautonomia of chronic fatigue syndrome. *J Electrocardiol.* 2006 Oct;39(4):389-94. PMID: 16895768

Relative short QTc intervals are features of the CFS-related dysautonomia.

*

Lerner AM, Dworkin HJ, Sayyed T, Chang CH, Fitzgerald JT, Beqaj S, Deeter RG, Goldstein J, Gottipolu P, O'Neill W. Prevalence of abnormal cardiac wall motion in the cardiomyopathy associated with incomplete multiplication of Epstein-barr Virus and/or cytomegalovirus in patients with chronic fatigue syndrome. *In Vivo.* 2004 Jul- Aug;18(4):417-24. PMID: 15369178

The prevalence of abnormal cardiac wall motion (ACWM) at rest in CFS patients was 10 out of 87 patients (11.5%). With stress exercise, 21 patients (24.1%) demonstrated ACWM. Cardiac biopsies in 3 of these CFS patients with ACWM showed a cardiomyopathy. Among the controls, ACWM at rest was present in 4 out of 191 patients (2%) (p=0.0018).

*

Peckerman A, LaManca JJ, Dahl KA, Chemitiganti R, Qureishi B, Natelson BH. Abnormal impedance cardiography predicts symptom severity in chronic fatigue syndrome. *Am J Med Sci.* 2003 Aug;326(2):55-60. PMID: 12920435

The patients with severe CFS had significantly lower stroke volume and cardiac output than the controls and less ill patients. Postexertional fatigue and flu-like symptoms of infection differentiated the patients with severe CFS from those with less severe CFS (88.5% concordance) and were predictive (R² = 0.46, P < 0.0002) of lower cardiac output. In contrast, neuropsychiatric symptoms showed no specific association with cardiac output.

*

Dworkin HJ, Lawrie C, Bohdiewicz P, Lerner AM. Abnormal left ventricular myocardial dynamics in eleven patients with chronic fatigue syndrome. *Clin Nucl Med.* 1994 Aug;19(8):675-7. PMID: 7955743

Eleven patients diagnosed with chronic fatigue syndrome were found to have abnormal left ventricular myocardial dynamics as indicated on MUGA studies. Among the abnormalities noted were abnormal wall motion at rest and stress, dilatation of the left ventricle, and segmental wall motion abnormalities.

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Lerner AM, Lawrie C, Dworkin HS. Repetitively negative changing T waves at 24-h electrocardiographic monitors in patients with the chronic fatigue syndrome. Left ventricular dysfunction in a cohort. *Chest*. 1993 Nov;104(5):1417-21. PMID: 8222798

A group of patients with CFS (age 50 or younger, no risk factors for coronary artery disease) all had abnormal Holter readings, while 22.4 percent patients without CFS had abnormal readings ($p < 0.01$). Mild left ventricular dysfunction was noted in 8 of 60 patients. All 60 showed repetitively flat to inverted T waves alternating with normal T waves. Stress multiple gated acquisitions (MUGAs) (labeled erythrocytes with stannous pyrophosphate) were abnormal in eight patients. Although resting ejection fractions (EFs) were normal, with increasing work loads, gross left ventricular dysfunction occurred.

Orthostatic Intolerance

Van Cauwenbergh D, Nijs J, Kos D, Van Weijnen L, Struyf F, Meeus M. Malfunctioning of the autonomic nervous system in patients with chronic fatigue syndrome: a systematic literature review. *Eur J Clin Invest*. 2014 May;44(5):516-26. PMID: 24601948

Via a systematic literature review, the authors concluded that there are differences in autonomous response between patients with CFS and healthy controls. The heart rate dynamic response during the head-up tilt test differs between patients with CFS and healthy controls, supporting the increased prevalence of postural orthostatic tachycardia syndrome.

*

Reynolds GK, Lewis DP, Richardson AM, Lidbury BA. Comorbidity of postural orthostatic tachycardia syndrome and chronic fatigue syndrome in an Australian cohort. *J Intern Med*. 2014 Apr;275(4):409-17. PMID: 24206536

In an Australian sample of CFS patients, 11% also suffered from POTS. CFS-POTS patients were significantly younger, had a shorter length of illness, experienced greater task difficulty and were able to stand for significantly shorter periods compared to the CFS-only patients. CFS-POTS patients experienced significantly lower baseline diastolic blood pressure, significantly higher heart rate and lower pulse pressures at each standing measurement. Early heart rate changes and overall heart rate change were significant predictors of completion status, whereas heart rate variability and female gender were significant predictors of increased perceived task difficulty.

*

Nijs J, Ickmans K. Postural orthostatic tachycardia syndrome as a clinically important subgroup of chronic fatigue syndrome: further evidence for central nervous system dysfunctioning. *J Intern Med*. 2013 May;273(5):498-500. PMID: 23331489

Postural orthostatic tachycardia syndrome and its relationship to CFS is discussed.

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Lewis I, Pairman J, Spickett G, Newton JL. Clinical characteristics of a novel subgroup of chronic fatigue syndrome patients with postural orthostatic tachycardia syndrome. *J Intern Med.* 2013 May;273(5):501-10. PMID: 23206180

CFS patients with POTS (13% of this sample) were younger, less fatigued, less depressed and had reduced daytime hypersomnolence, compared with patients without POTS. In addition, they exhibited greater orthostatic intolerance and autonomic dysfunction.

*

Okamoto LE, Raj SR, Peltier A, Gamboa A, Shibao C, Diedrich A, Black BK, Robertson D, Biaggioni I. Neurohumoral and haemodynamic profile in postural tachycardia and chronic fatigue syndromes. *Clin Sci (Lond).* 2012 Feb 1;122(4):183-92. PMID: 21906029

The authors compared CFS and POTS (postural tachycardia syndrome) patients, concluding that most POTS patients met the criteria for CFS. CFS-POTS patients have higher markers of sympathetic activation, but are part of the spectrum of POTS. Targeting this sympathetic activation should be considered in the treatment of these patients.

*

Benarroch EE. Postural tachycardia syndrome: a heterogeneous and multifactorial disorder. *Mayo Clin Proc.* 2012 Dec;87(12):1214-25. PMID: 23122672

This paper provides a literature review on postural tachycardia syndrome (POTS), including its role in CFS.

*

Allen J, Murray A, Di Maria C, Newton JL. Chronic fatigue syndrome and impaired peripheral pulse characteristics on orthostasis--a new potential diagnostic biomarker. *Physiol Meas.* 2012 Feb;33(2):231-41. PMID: 22273713

The researchers explored the clinical value of non-invasive optical multi-site photoplethysmography (PPG) technology to assess cardiovascular responses to standing.

*

Ocon AJ, Messer Z, Medow M, Stewart J. Increasing orthostatic stress impairs neurocognitive functioning in Chronic Fatigue Syndrome with Postural Tachycardia Syndrome. *Clin Sci (Lond).* 2011 Sep 15. PMID: 21919887

Increasing orthostatic stress combined with a cognitive challenge impairs the neurocognitive abilities of working memory, accuracy, and information processing in CFS/postural orthostatic tachycardia syndrome, but this is not related to changes in cerebral blood flow velocity. Individuals with CFS/POTS should be aware that orthostatic stress may impair their neurocognitive abilities.

*

Jones DE, Gray J, Frith J, Newton JL. Fatigue severity remains stable over time and independently associated with orthostatic symptoms in chronic fatigue syndrome: a longitudinal study. *J Intern Med.* 2011 Feb;269(2):182-8. PMID: 21073560

In CFS patients, intolerance is correlated with fatigue, and fatigue is worse in mornings than later in the

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day.

*

Wyller VB, Barbieri R, Saul JP. Blood pressure variability and closed-loop baroreflex assessment in adolescent chronic fatigue syndrome during supine rest and orthostatic stress. *Eur J Appl Physiol.* 2011 Mar;111(3):497-507. PMID: 20890710

CFS in adolescents is characterized by reduced systolic blood pressure variability and a sympathetic predominance of baroreflex heart rate control during orthostatic stress.

*

Costigan A, Elliott C, McDonald C, Newton JL. Orthostatic symptoms predict functional capacity in chronic fatigue syndrome: implications for management. *QJM.* 2010 Jun 9. PMID: 20534655

Treatment of orthostatic symptoms in CFS has the potential to improve functional capacity and quality of life.

*

Hollingsworth KG, Jones DE, Taylor R, Blamire AM, Newton JL. *Eur J Clin Invest.* Impaired cardiovascular response to standing in Chronic Fatigue Syndrome. 2010 May 20. PMID: 20497461

Heart problems in CFS cause orthostatic intolerance, meaning that symptoms get worse when standing up.

*

Wyller VB, Barbieri R, Thaulow E, Saul JP. Enhanced vagal withdrawal during mild orthostatic stress in adolescents with chronic fatigue. *Ann Noninvasive Electrocardiol.* 2008 Jan;13(1):67-73. PMID: 18234008

CFS patients have heart problems, emerging during mild orthostatic stress. Possible underlying mechanisms include low blood volume and abnormalities of reflex mechanisms.

*

Hoad A, Spickett G, Elliott J, Newton J. Postural orthostatic tachycardia syndrome is an under-recognized condition in chronic fatigue syndrome. *QJM.* 2008 Dec;101(12):961-5. PMID: 18805903

Postural orthostatic tachycardia syndrome (POTS), with abnormally high heart rate on standing, is a frequent finding in patients with CFS/ME and results in fatigue.

*

Galland BC, Jackson PM, Sayers RM, Taylor BJ. A matched case control study of orthostatic intolerance in children/adolescents with chronic fatigue syndrome. *Pediatr Res.* 2008 Feb;63(2):196-202. PMID: 18091356

CFS patients were more susceptible to orthostatic intolerance, with the unique manifestation of postural orthostatic tachycardia syndrome.

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Wyller VB, Saul JP, Walløe L, Thaulow E. Sympathetic cardiovascular control during orthostatic stress and isometric exercise in adolescent chronic fatigue syndrome. *Eur J Appl Physiol.* 2008 Apr;102(6):623-32. PMID: 18066580

Adolescents with CFS have increased sympathetic activity at rest with exaggerated cardiovascular response to orthostatic stress, but attenuated cardiovascular response when performing isometric exercise during orthostatic stress.

*

Agarwal AK, Garg R, Ritch A, Sarkar P. Postural orthostatic tachycardia syndrome. *Postgrad Med J.* 2007 Jul;83(981):478-80. PMID: 17621618

The clinical picture, diagnosis, and management of POTS are discussed.

*

Wyller VB, Saul JP, Amlie JP, Thaulow E. Sympathetic predominance of cardiovascular regulation during mild orthostatic stress in adolescents with chronic fatigue. *Clin Physiol Funct Imaging.* 2007 Jul;27(4):231-8. PMID: 17564672

Adolescents with CFS have sympathetic predominance of cardiovascular regulation during very mild orthostatic stress.

*

Tanaka H. Autonomic function and child chronic fatigue syndrome. *Nihon Rinsho.* 2007 Jun;65(6):1105-12. PMID: 17561705

Autonomic function might be partly involved in CFS such as orthostatic dysfunction, but its priority in causing CFS is unclear.

*

Natelson BH, Intriligator R, Cherniack NS, Chandler HK, Stewart JM. Hypocapnia is a biological marker for orthostatic intolerance in some patients with chronic fatigue syndrome. *Dyn Med.* 2007 Jan 30;6:2. PMID: 17263876

A substantial number of CFS patients have orthostatic intolerance in the form of orthostatic hypocapnia.

*

Naschitz JE, Yeshurun D, Rosner I. Dysautonomia in chronic fatigue syndrome: facts, hypotheses, implications. *Med Hypotheses.* 2004;62(2):203-6. PMID: 14962627

The authors hypothesize that dysautonomia is pivotal in the pathophysiology CFS and that manipulating the autonomic nervous system may be an effective treatment.

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Peckerman A, LaManca JJ, Qureishi B, Dahl KA, Golfetti R, Yamamoto Y, Natelson BH. Baroreceptor reflex and integrative stress responses in chronic fatigue syndrome. *Psychosom Med.* 2003 Sep-Oct;65(5):889-95. PMID: 14508037

In CFS, deficiencies in orthostatic regulation, but not in centrally mediated stress responses, may involve the baroreceptor reflex.

*

Khan F, Spence V, Kennedy G, Belch JJ. Prolonged acetylcholine-induced vasodilatation in the peripheral microcirculation of patients with chronic fatigue syndrome. *Clin Physiol Funct Imaging.* 2003 Sep;23(5):282-5. PMID: 12950326

Prolongation of acetylcholine-induced vasodilatation is suggestive of a disturbance to cholinergic pathways, perhaps within the vascular endothelium of patients with CFS, and might be related to some of the unusual vascular symptoms, such as hypotension and orthostatic intolerance, which are characteristic of the condition.

*

Tanaka H, Matsushima R, Tamai H, Kajimoto Y. Impaired postural cerebral hemodynamics in young patients with chronic fatigue with and without orthostatic intolerance. *J Pediatr.* 2002 Apr;140(4):412-7. PMID: 12006954

In a study of CFS patients, orthostatic intolerance determined by cardiovascular responses to standing was observed in 16 of 28 patients: instantaneous orthostatic hypotension in 8, delayed orthostatic hypotension in 2, and postural orthostatic tachycardia in 6. A rapid recovery of oxy-Hb by near infrared spectroscopy at the onset of active standing was not found in 15 of 16 patients with chronic fatigue and orthostatic intolerance and in 6 of 12 patients with chronic fatigue without orthostatic intolerance but only in 2 of 20 control subjects. Thirteen of 16 patients with orthostatic intolerance showed prolonged reduction in oxy-Hb during standing.

*

Naschitz JE, Sabo E, Naschitz S, Shaviv N, Rosner I, Rozenbaum M, Gaitini L, Ahdoot A, Ahdoot M, Priselac RM, Eldar S, Zukerman E, Yeshurun D. Hemodynamic instability in chronic fatigue syndrome: indices and diagnostic significance. *Semin Arthritis Rheum.* 2001 Dec;31(3):199-208. PMID: 11740800

The hemodynamic instability score, related to cardiovascular response to postural challenge, adds objective criteria confirming the diagnosis of CFS.

*

Stewart JM. Autonomic nervous system dysfunction in adolescents with postural orthostatic tachycardia syndrome and chronic fatigue syndrome is characterized by attenuated vagal baroreflex and potentiated sympathetic vasomotion. *Pediatr Res.* 2000 Aug;48(2):218-26. PMID: 10926298

Heart rate and blood pressure regulation in POTS and CFS patients are similar and indicate attenuated efferent vagal baroreflex associated with increased vasomotor tone. Loss of beat-to-beat heart rate control may contribute to a destabilized blood pressure resulting in orthostatic intolerance.

Appendix of Comments

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Streeten DH, Thomas D, Bell DS. The roles of orthostatic hypotension, orthostatic tachycardia, and subnormal erythrocyte volume in the pathogenesis of the chronic fatigue syndrome. *Am J Med Sci.* 2000 Jul;320(1):1-8. PMID: 10910366

Delayed orthostatic hypotension and/or tachycardia caused by excessive gravitational venous pooling, which is correctable with external lower-body compression, together with subnormal circulating erythrocyte volume, are very frequent, although not invariably demonstrable, findings in moderate to severe CFS.

*

Rowe PC, Barron DF, Calkins H, Maumenee IH, Tong PY, Geraghty MT. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. *J Pediatr.* 1999 Oct;135(4):494-9. PMID: 10518084

Among patients with CFS and orthostatic intolerance, a subset also has Ehlers-Danlos syndrome.

*

Stewart JM, Gewitz MH, Weldon A, Munoz J. Patterns of orthostatic intolerance: the orthostatic tachycardia syndrome and adolescent chronic fatigue. *J Pediatr.* 1999 Aug;135(2 Pt 1):218-25. PMID: 10431117

Symptoms and patterns of orthostatic heart rate and blood pressure change in orthostatic tachycardia syndrome overlap strongly with those of CFS. Orthostatic intolerance in orthostatic tachycardia syndrome may represent an attenuated form of chronic fatigue pathophysiology.

*

Schondorf R, Benoit J, Wein T, Phaneuf D. Orthostatic intolerance in the chronic fatigue syndrome. *J Auton Nerv Syst.* 1999 Feb 15;75(2-3):192-201. PMID: 10189122

On average, the duration of disease and patient age were significantly less and the onset of symptoms was more often subacute in CFS patients with OI than in those without OI.

*

Stewart JM, Gewitz MH, Weldon A, Arlievsky N, Li K, Munoz J. Orthostatic intolerance in adolescent chronic fatigue syndrome. *Pediatrics.* 1999 Jan;103(1):116-21. PMID: 9917448

CFS is highly related to orthostatic intolerance in adolescents. The orthostatic intolerance of CFS often has heart rate and BP responses similar to responses in the syndrome of orthostatic tachycardia, suggesting that a partial autonomic defect may contribute to symptomatology in these patients.

*

Streeten DH, Anderson GH Jr. The role of delayed orthostatic hypotension in the pathogenesis of chronic fatigue. *Clin Auton Res.* 1998 Apr;8(2):119-24. PMID: 9613802

Fatigue is a very common symptom in patients with delayed orthostatic hypotension, as well as both primary and secondary hypocortisolism.

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Rowe PC, Calkins H. Neurally mediated hypotension and chronic fatigue syndrome. *Am J Med.* 1998 Sep 28;105(3A):15S-21S. PMID: 9790477

Patients with CFS have a high prevalence of neurally mediated hypotension, and open treatment of this autonomic dysfunction has been associated with improvements in CFS symptoms.

*

Rowe PC, Bou-Holaigah I, Kan JS, Calkins H. Is neurally mediated hypotension an unrecognized cause of chronic fatigue? *Lancet.* 1995 Mar 11;345(8950):623-4. PMID: 7898182

This study suggests an overlap in the symptoms of chronic fatigue syndrome and neurally mediated hypotension.

Tilt Table Test

Wyller VB, Due R, Saul JP, Amlie JP, Thaulow E. Usefulness of an abnormal cardiovascular response during low-grade head-up tilt-test for discriminating adolescents with chronic fatigue from healthy controls. *Am J Cardiol.* 2007 Apr 1;99(7):997-1001. PMID: 17398200

Adolescents with CFS have significant abnormalities of cardiovascular regulation in response to mild orthostatic stress.

*

Naschitz JE, Mussafia-Priselac R, Kovalev Y, Zaigaykin N, Slobodin G, Elias N, Rosner I. Patterns of hypocapnia on tilt in patients with fibromyalgia, chronic fatigue syndrome, nonspecific dizziness, and neurally mediated syncope. *Am J Med Sci.* 2006 Jun;331(6):295-303. PMID: 16775435

Hyperventilation appears to be the major abnormal response to postural challenge in sustained hypocapnia. Because unrecognized hypocapnia is common in CFS, fibromyalgia, and nonspecific dizziness, capnography should be a part of the evaluation of patients with such conditions.

*

Jones JF, Nicholson A, Nisenbaum R, Papanicolaou DA, Solomon L, Boneva R, Heim C, Reeves WC. Orthostatic instability in a population-based study of chronic fatigue syndrome. *Am J Med.* 2005 Dec;118(12):1415. PMID: 16378795

Orthostatic instability was similar in persons with chronic fatigue syndrome and nonfatigued controls subjects recruited from the general Wichita population. Delayed responses to head-up tilt tests were common and may reflect hydration status.

*

Yoshiuchi K, Quigley KS, Ohashi K, Yamamoto Y, Natelson BH. Use of time-frequency analysis to investigate temporal patterns of cardiac autonomic response during head-up tilt in chronic fatigue

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syndrome. *Auton Neurosci*. 2004 Jun 30;113(1-2):55-62. PMID: 15296795

We studied 18 CFS patients without POTS, eight CFS patients with POTS and 25 sedentary healthy controls during supine rest and during the first 10 min after HUT. Even CFS patients without POTS may have a subtle underlying disturbance in autonomic function.

*

Razumovsky AY, DeBusk K, Calkins H, Snader S, Lucas KE, Vyas P, Hanley DF, Rowe PC. Cerebral and systemic hemodynamics changes during upright tilt in chronic fatigue syndrome. *J Neuroimaging*. 2003 Jan;13(1):57-67. PMID: 12593133

Patients with CFS did not have abnormal cerebral blood flow velocity (CBFV) compared with controls in response to orthostatic stress. The median time to hypotension did not differ, but the median time to onset of orthostatic symptoms was shorter in those with CFS.

*

Yamamoto Y, LaManca JJ, Natelson BH. A measure of heart rate variability is sensitive to orthostatic challenge in women with chronic fatigue syndrome. *Exp Biol Med (Maywood)*. 2003 Feb;228(2):167-74. PMID: 12563023

This study suggests that a decrease in aperiodic fractal component of heart rate variability in response to head up tilt can be used to differentiate patients with CFS from controls.

*

Naschitz JE, Rosner I, Rozenbaum M, Naschitz S, Musafia-Priselac R, Shaviv N, Fields M, Isseroff H, Zuckerman E, Yeshurun D, Sabo E. The head-up tilt test with haemodynamic instability score in diagnosing chronic fatigue syndrome. *QJM*. 2003 Feb;96(2):133-42. PMID: 12589011

The authors developed a method that uses a head-up tilt test (HUTT) to estimate blood pressure and heart rate instability during tilt. There is a particular dysautonomia in CFS that differs from dysautonomia in other disorders, characterized by haemodynamic instability score > 0.98. This can reinforce the clinician's diagnosis by providing objective criteria for the assessment of CFS.

*

Timmers HJ, Wieling W, Soetekouw PM, Bleijenberg G, Van Der Meer JW, Lenders JW. Hemodynamic and neurohumoral responses to head-up tilt in patients with chronic fatigue syndrome. *Clin Auton Res*. 2002 Aug;12(4):273-80. PMID: 12357281

Head-up tilt evokes postural tachycardia or (pre)syncope in a minority of CFS patients. In this study, head-up tilt-negative CFS patients had a higher heart rate at baseline together with a marked decrease in stroke volume in response to head-up tilt.

*

Naschitz JE, Rozenbaum M, Rosner I, Sabo E, Priselac RM, Shaviv N, Ahdoot A, Ahdoot M, Gaitini L, Eldar S, Yeshurun D. Cardiovascular response to upright tilt in fibromyalgia differs from that in chronic fatigue syndrome. *J Rheumatol*. 2001 Jun;28(6):1356-60. PMID: 11409131

Cardiovascular response during postural challenge were more problematic in CFS patients than in healthy controls or than in fibromyalgia patients.

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Karas B, Grubb BP, Boehm K, Kip K. The postural orthostatic tachycardia syndrome: a potentially treatable cause of chronic fatigue, exercise intolerance, and cognitive impairment in adolescents. *Pacing Clin Electrophysiol.* 2000 Mar;23(3):344-51. PMID: 10750135

POTS may occur in adolescents and represents a mild, potentially treatable form of autonomic dysfunction that can be readily identified during head upright tilt table testing.

*

LaManca JJ, Peckerman A, Walker J, Kesil W, Cook S, Taylor A, Natelson BH. Cardiovascular response during head-up tilt in chronic fatigue syndrome. *Clin Physiol.* 1999 Mar;19(2):111-20. PMID: 10200892

This study examined the cardiovascular response to orthostatic challenge, noting differences between patients and controls.

*

Stewart J, Weldon A, Arlievsky N, Li K, Munoz J. Neurally mediated hypotension and autonomic dysfunction measured by heart rate variability during head-up tilt testing in children with chronic fatigue syndrome. *Clin Auton Res.* 1998 Aug;8(4):221-30. PMID: 9791743

In a tilt table test, 81% of CFS patients fainted, compared to 30% of controls. Heart rate variability indices were strikingly decreased in CFS patients. These data may indicate autonomic impairment in patients with CFS.

*

De Becker P, Dendale P, De Meirleir K, Campine I, Vandeborne K, Hagers Y. Autonomic testing in patients with chronic fatigue syndrome. *Am J Med.* 1998 Sep 28;105(3A):22S- 26S. PMID: 9790478

After a tilt table test, CFS patients had abnormally high heart rates and abnormally low frequency power.

*

De Lorenzo F, Hargreaves J, Kakkar VV. Pathogenesis and management of delayed orthostatic hypotension in patients with chronic fatigue syndrome. *Clin Auton Res.* 1997 Aug;7(4):185-90. PMID: 9292244

An abnormal response to upright tilt was observed in 22 of 78 patients with CFS. After sodium chloride therapy for 8 weeks, half of patients did not show an abnormal response to the test and reported improvement in CFS symptoms. Patients who did not respond to sodium chloride therapy were found to have low plasma renin activity.

*

Freeman R, Komaroff AL. Does the chronic fatigue syndrome involve the autonomic nervous system? *Am J Med.* 1997 Apr;102(4):357-64. PMID: 9217617

CFS subjects had a significant increase in baseline and maximum heart rate (HR) on standing and a tilt table test. Tests of parasympathetic nervous system function were significantly less in the CFS group as

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were measures of sympathetic nervous system function. Twenty-five percent of CFS subjects had a positive tilt table test. The physical activity index was a significant predictor of autonomic test results; and the blood pressure decrease in phase II of the Valsalva maneuver, whereas premorbid and coexistent psychiatric conditions were not. The onset of autonomic symptoms occurred within 4 weeks of a viral infection in 46% of patients—a temporal pattern that is consistent with a postviral, idiopathic autonomic neuropathy.

*

De Lorenzo F, Hargreaves J, Kakkar VV. Possible relationship between chronic fatigue and postural tachycardia syndromes. *Clin Auton Res*. 1996 Oct;6(5):263-4. PMID: 8899252

Upright tilt-table testing induced significant hypotension and increased heart rate in a group of five CFS patients.

*

Bou-Halaigah I, Rowe PC, Kan J, Calkins H. The relationship between neurally mediated hypotension and the chronic fatigue syndrome. *JAMA*. 1995 Sep 27;274(12):961-7. PMID: 7674527

An abnormal response to upright tilt was observed in 22 of 23 patients with chronic fatigue syndrome vs four of 14 controls ($P < .001$). Seventy percent of chronic fatigue syndrome patients, but no controls, had an abnormal response during stage 1 ($P < .001$). Nine patients reported complete or nearly complete resolution of chronic fatigue syndrome symptoms after therapy directed at neurally mediated hypotension.

Other Cardiovascular Issues

Gao J, Gurbaxani BM, Hu J, Heilman KJ, Emanuele II VA, Lewis GF, Davila M, Unger ER, Lin JM. Multiscale analysis of heart rate variability in non-stationary environments. *Front Physiol*. 2013 May 30;4:119. PMID: 23755016

Multiscale analyses suggested that there are notable differences in heart rate variability between CFS patients and matched controls before a social stress test, but that these differences seemed to diminish during the test.

*

Meeus M, Goubert D, De Backer F, Struyf F, Hermans L, Coppieters I, De Wandele I, Da Silva H, Calders P. Heart rate variability in patients with fibromyalgia and patients with chronic fatigue syndrome: A systematic review. *Semin Arthritis Rheum*. 2013 Oct;43(2):279-87. PMID: 23838093

Fibromyalgia patients show more heart rate variability aberrances and indices of increased sympathetic activity. Increased sympathetic activity is only present in CFS patients at night.

*

Hurum H, Sulheim D, Thaulow E, Wyller VB. Elevated nocturnal blood pressure and heart rate in adolescent chronic fatigue syndrome. *Acta Paediatr*. 2011 Feb;100(2):289-92. PMID: 21059182

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In adolescent CFS patients at night, heart rate, arterial blood pressure and diastolic blood pressure were higher than normal; during daytime, heart rate was higher than normal but both blood pressure readings were normal.

*

Burton AR, Rahman K, Kadota Y, Lloyd A, Vollmer-Conna U. Reduced heart rate variability predicts poor sleep quality in a case-control study of chronic fatigue syndrome. *Exp Brain Res*. 2010 Jul;204(1):71-8. PMID: 20502886

This study identified significant reductions in vagal modulation of heart rate during sleep in CFS. Low heart rate variance strongly predicted sleep quality-suggesting a pervasive state of nocturnal sympathetic hypervigilance in CFS.

*

Newton JL, Sheth A, Shin J, Pairman J, Wilton K, Burt JA, Jones DE. Lower ambulatory blood pressure in chronic fatigue syndrome. *Psychosom Med*. 2009 Apr;71(3):361-5. PMID: 19297309

CFS patients have lower blood pressure and abnormal blood pressure regulation.

*

Newton JL, Okonkwo O, Sutcliffe K, Seth A, Shin J, Jones DE. Symptoms of autonomic dysfunction in chronic fatigue syndrome. *QJM*. 2007 Aug;100(8):519-26. PMID: 17617647

Symptoms of autonomic dysfunction were associated with CFS and correlated with the severity of the fatigue.

*

Boneva RS, Decker MJ, Maloney EM, Lin JM, Jones JF, Helgason HG, Heim CM, Rye DB, Reeves WC. Higher heart rate and reduced heart rate variability persist during sleep in chronic fatigue syndrome: a population-based study. *Auton Neurosci*. 2007 Dec 30;137(1-2):94-101. PMID: 17851136

The presence of increased heart rate and reduced heart rate variability in CFS during sleep coupled with higher norepinephrine levels and lower plasma aldosterone suggest a state of sympathetic ANS predominance and neuroendocrine alterations.

*

Winkler AS, Blair D, Marsden JT, Peters TJ, Wessely S, Cleare AJ. Autonomic function and serum erythropoietin levels in chronic fatigue syndrome. *J Psychosom Res*. 2004 Feb;56(2):179-83. PMID:15016575

Autonomic testing in patients with chronic fatigue syndrome yielded a significantly greater increase in heart rate together with a more pronounced systolic blood pressure fall on standing compared to healthy individuals. Heart rate beat-to-beat variation on deep breathing and responses to the Valsalva manoeuvre were normal. Serum erythropoietin levels were within reference range.

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Vanness JM, Snell CR, Strayer DR, Dempsey L 4th, Stevens SR. Subclassifying chronic fatigue syndrome through exercise testing. *Med Sci Sports Exerc.* 2003 Jun;35(6):908-13. PMID: 12783037

On a graded exercise test, significant differences were found between impairment levels of CFS patients for percentage of predicted [OV0312]O₂ and peak heart rate.

*

Naschitz JE, Sabo E, Naschitz S, Rosner I, Rozenbaum M, Fields M, Isseroff H, Priselac RM, Gaitini L, Eldar S, Zukerman E, Yeshurun D. Hemodynamics instability score in chronic fatigue syndrome and in non-chronic fatigue syndrome. *Semin Arthritis Rheum.* 2002 Dec;32(3):141-8. PMID: 12528078

The cardiovascular reactivity in patients with CFS has certain features in common with the reactivity in patients with recurrent syncope or non-CFS chronic fatigue, such as the frequent occurrence of vasodepressor reaction, cardioinhibitory reaction, and postural tachycardia syndrome. Apart from to these shared responses, the large majority of CFS

patients exhibit a particular abnormality which is characterized by hemodynamic instability score values >0.98, lending objective criteria to the assessment of CFS.

*

Naschitz JE, Sabo E, Naschitz S, Rosner I, Rozenbaum M, Priselac RM, Gaitini L, Zukerman E, Yeshurun D. Fractal analysis and recurrence quantification analysis of heart rate and pulse transit time for diagnosing chronic fatigue syndrome. *Clin Auton Res.* 2002 Aug;12(4):264-72. PMID: 12357280

This study aimed to develop a method to distinguish between the cardiovascular reactivity in chronic fatigue syndrome (CFS) and other patient populations. The authors found that the best cut-off distinguishing CFS patients from others was the Fractal & Recurrence Analysis-based Score, which has potential as a diagnostic.

*

Farquhar WB, Hunt BE, Taylor JA, Darling SE, Freeman R. Blood volume and its relation to peak O₂ consumption and physical activity in patients with chronic fatigue. *Am J Physiol Heart Circ Physiol.* 2002 Jan;282(1):H66-71. PMID: 11748048

Individuals with CFS have a significantly lower peak oxygen consumption and an insignificant trend toward lower blood volume compared with controls. These two factors are highly related to one another.

*

LaManca JJ, Peckerman A, Sisto SA, DeLuca J, Cook S, Natelson BH. Cardiovascular responses of women with chronic fatigue syndrome to stressful cognitive testing before and after strenuous exercise. *Psychosom Med.* 2001 Sep-Oct;63(5):756-64. PMID: 11573024

Women with CFS have a diminished cardiovascular response to cognitive stress. Patients with the lowest cardiovascular reactivity had the highest ratings of CFS symptom severity.

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Duprez DA, De Buyzere ML, Drieghe B, Vanhaverbeke F, Taes Y, Michielsen W, Clement DL. Long- and short-term blood pressure and RR-interval variability and psychosomatic distress in chronic fatigue syndrome. *Clin Sci (Lond)*. 1998 Jan;94(1):57-63. PMID: 9505867

CFS patients had higher heart rates and (in supine position) lower spectral indices of blood pressure variability than normal people.

*

Cordero DL, Sisto SA, Tapp WN, LaManca JJ, Pareja JG, Natelson BH. Decreased vagal power during treadmill walking in patients with chronic fatigue syndrome. *Clin Auton Res*. 1996 Dec;6(6):329-33. PMID: 8985621

CFS patients have a subtle abnormality in vagal activity to the heart that may explain, in part, their post-exertional symptom exacerbation.

*

Montague TJ, Marrie TJ, Klassen GA, Bewick DJ, Horacek BM. Cardiac function at rest and with exercise in the chronic fatigue syndrome. *Chest*. 1989 Apr;95(4):779-84. PMID: 2924607

Patients with CFS have normal resting cardiac function but a markedly abbreviated exercise capacity characterized by slow acceleration of heart rate and fatigue of exercising muscles long before peak heart rate is achieved.

Exercise & Activity Intolerance

Keller BA, Pryor JL, Giloteaux L. Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO₂peak indicates functional impairment. *J Transl Med*. 2014 Apr 23;12(1):104. PMID: 24755065

The study looked at repeat cardiopulmonary exercise tests (CPET) done on two consecutive days. Compared to healthy controls, a group of ME/CFS patients showed significant decreases from Day 1 to Day 2 in oxygen consumption (VO₂) peak, heart rate (HR) peak, minute ventilation (V_e) peak, and workload (Work) at peak. Decreases in ventilatory threshold (VT) measures included VO₂@VT (15.8%), V_e@VT (7.4%), and Work@VT (21.3%). Peak respiratory exchange ratio was high and did not differ between tests, indicating maximum effort by participants during both CPETs. If data from only a single CPET test is used, a standard classification of functional impairment based on VO₂peak or VO₂@VT results in over-estimation of functional ability for 50% of ME/CFS participants in this study.

*

Vermeulen RC, Vermeulen van Eck IW. Decreased oxygen extraction during cardiopulmonary exercise test in patients with chronic fatigue syndrome. *J Transl Med*. 2014 Jan 23;12:20. PMID: 24456560

The authors analysed the cardiopulmonary exercise tests of CFS patients, idiopathic chronic fatigue (CFI) patients and healthy visitors. They concluded that low oxygen uptake by muscle cells causes exercise

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intolerance in a majority of CFS patients,

indicating insufficient metabolic adaptation to incremental exercise. They also stated that the high increase of the cardiac output relative to the increase of oxygen uptake argues against deconditioning as a cause for physical impairment in these patients.

*

Kishi A, Togo F, Cook DB, Klapholz M, Yamamoto Y, Rapoport DM, Natelson BH. The effects of exercise on dynamic sleep morphology in healthy controls and patients with chronic fatigue syndrome. *Physiol Rep*. 2013 Nov;1(6):e00152. PMID: 24400154

Compared to controls, CFS patients demonstrated a higher level of sleep abnormalities subsequent to exercise.

*

Snell CR, Stevens SR, Davenport TE, Van Ness JM. Discriminative validity of metabolic and workload measurements for identifying people with chronic fatigue syndrome. *Phys Ther*. 2013 Nov;93(11):1484-92. PMID: 23813081

The objective of this study was to determine the discriminative validity of objective measurements obtained during cardiopulmonary exercise testing to distinguish participants with CFS from participants who did not have a disability but were sedentary. The lack of any significant differences between groups for the first exercise test would appear to support a deconditioning hypothesis for CFS symptoms. However, the results from the second test indicated the presence of CFS-related postexertion fatigue.

*

Strahler J, Fischer S, Nater UM, Ehlert U, Gaab J. Norepinephrine and epinephrine responses to physiological and pharmacological stimulation in chronic fatigue syndrome. *Biol Psychol*. 2013 Sep;94(1):160-6. PMID: 23770415

The researchers found evidence of altered sympathetic-neural and sympathetic adrenomedulla reactivity in CFS. Exercise stress revealed a subtle catecholaminergic hyporeactivity in CFS patients.

*

Nakamura T, Schwander S, Donnelly R, Cook DB, Ortega F, Togo F, Yamamoto Y, Cherniack NS, Klapholz M, Rapoport D, Natelson BH. Exercise and sleep deprivation do not change cytokine expression levels in patients with chronic fatigue syndrome. *Clin Vaccine Immunol*. 2013 Nov;20(11):1736-42. PMID: 24027260

The researchers conducted repeat blood sampling for cytokine levels from healthy subjects and CFS patients during both postexercise and total sleep deprivation nights and assayed for protein levels in the blood samples, mRNA activity in peripheral blood

lymphocytes (PBLs), and function in resting and stimulated PBLs. They found that these environmental manipulations did not produce clinically significant upregulation of proinflammatory cytokines.

*

White AT, Light AR, Hughen RW, Vanhaisma TA, Light KC. Differences in metabolite- detecting, adrenergic, and immune gene expression after moderate exercise in patients with chronic fatigue syndrome, patients with multiple sclerosis, and healthy controls.

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Psychosom Med. 2012 Jan;74(1):46-54. PMID: 22210239

Postexercise mRNA increases in metabolite-detecting receptors were unique to patients with CFS, whereas both patients with MS and patients with CFS showed abnormal increases in adrenergic receptors. Among patients with MS, greater fatigue was correlated with blunted immune marker expression.

*

Cook DB, Stegner AJ, Nagelkirk PR, Meyer JD, Togo F, Natelson BH. Responses to exercise differ for chronic fatigue syndrome patients with fibromyalgia. *Med Sci Sports Exerc.* 2012 Jun;44(6):1186-93. PMID: 22157881

The purpose of the present study was to examine cardiac and perceptual responses to steady-state submaximal exercise in CFS patients and healthy controls. The CFS + FM group exhibited an exercise response characterized by higher stroke index, ventilatory equivalents for oxygen and carbon dioxide and rating of perceived exertion, lower systolic blood pressure, and similar HR responses compared to controls.

*

Jammes Y, Steinberg JG, Delliaux S. Chronic fatigue syndrome: acute infection and history of physical activity affect resting levels and response to exercise of plasma oxidant/antioxidant status and heat shock proteins. *J Intern Med.* 2011 Nov 24. PMID: 22112145

The presence of stress factors in the history of CFS patients is associated with severe oxidative stress and the suppression of protective HSP27 and HSP70 responses to exercise.

*

Jones DE, Hollingsworth KG, Jakovljevic DG, Fattakhova G, Pairman J, Blamire AM, Trenell MI, Newton JL. Loss of capacity to recover from acidosis on repeat exercise in chronic fatigue syndrome: a case-control study. *Eur J Clin Invest.* 2011 Jun 10. PMID: 21749371

CFS patients exhibit "profound abnormality in bioenergetic function." When they exercise at the level of normal people, they demonstrate increased intramuscular acidosis that does not decrease normally with repeated exercise. Compared to normal people, it also takes four times as long for their pH to return to baseline after exercise.

*

Nijs J, Meeus M, Van Oosterwijck J, Ickmans K, Moorkens G, Hans G, De Clerck LS. In the mind or in the brain? Scientific evidence for central sensitisation in chronic fatigue syndrome. *Eur J Clin Invest.* 2011 Jul 2. PMID: 21793823

CFS patients suffer from hyperresponsiveness of the central nervous system to various stimuli, including heat, mechanical pressure, electrical stimulation and histamine. Exercise worsens this tendency.

*

Light AR, Bateman L, Jo D, Hughen RW, Vanhaisma TA, White AT, Light KC. Gene expression alterations at baseline and following moderate exercise in patients with Chronic Fatigue Syndrome and Fibromyalgia Syndrome. *J Intern Med.* 2011 May 26. PMID: 21615807

CFS patients exhibited two different abnormal responses to exercise. Some patients demonstrated

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abnormal increases in mRNA for sensory and adrenergic receptors and a cytokine, resulting in fatigue or pain. A second group demonstrated abnormal decreases in adrenergic α -2A receptor's transcription. None of the normal patients in the study showed these responses, and the authors thus suggest that this finding has the potential of serving as a biomarker for the disease.

*

Davenport TE, Stevens SR, Baroni K, Van Ness M, Snell CR. Diagnostic accuracy of symptoms characterising chronic fatigue syndrome. *Disabil Rehabil.* 2011 Jan 6. PMID: 21208154

Presence of just three measures (fatigue, sleep and pain) was effective in predicting exercise intolerance -- a definitional indicator of CFS status.

*

Vermeulen RC, Kurk RM, Visser FC, Sluiter W, Scholte HR. Patients with chronic fatigue syndrome performed worse than controls in a controlled repeated exercise study despite a normal oxidative phosphorylation capacity. *J Transl Med.* 2010 Oct 11;8:93.

CFS patients reached the anaerobic threshold and the maximal exercise at a much lower oxygen consumption than the controls, and this worsened in the second test. This implies

an increase of lactate, the product of anaerobic glycolysis, and a decrease of the mitochondrial ATP production in the patients.

*

Meeus M, Ickmans K, De Clerck LS, Moorkens G, Hans G, Grosemans S, Nijs J. Serotonergic descending inhibition in chronic pain: design, preliminary results and early cessation of a randomized controlled trial. *In Vivo.* 2011 Nov-Dec;25(6):1019-25. PMID: 22021700

The authors administered the antidepressant citalopram to CFS patients and then had them perform a submaximal exercise protocol, preceded and followed by an assessment of endogenous pain inhibition. Significant negative effects were observed in all patients and the authors decided that proceeding with the study would be unethical.

*

Meeus M, Roussel NA, Truijen S, Nijs J. Reduced pressure pain thresholds in response to exercise in chronic fatigue syndrome but not in chronic low back pain: an experimental study. *J Rehabil Med.* 2010 Oct;42(9):884-90. PMID: 20878051

CFS patients show hyperalgesia and abnormal central pain processing during submaximal aerobic exercise.

*

Meeus M, van Eupen I, van Baarle E, De Boeck V, Luyckx A, Kos D, Nijs J. Symptom fluctuations and daily physical activity in patients with chronic fatigue syndrome: a case-control study. *Arch Phys Med Rehabil.* 2011 Nov;92(11):1820-6. PMID: 22032215

The more that patients with CFS are sedentary and the better activity is dispersed, the fewer symptoms and variations they experience on the same and next day. Inversely, more symptoms and variability is experienced when patients were more active that day or the previous day.

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Suárez A, Guillamo E, Roig T, Blázquez A, Alegre J, Bermúdez J, Ventura JL, García- Quintana AM, Comella A, Segura R, Javierre C. Nitric Oxide Metabolite Production During Exercise in Chronic Fatigue Syndrome: A Case-Control Study. *J Womens Health (Larchmt)*. 2010 May 14. PMID: 20469961

CFS patients had a higher increase in nitric oxide metabolites after exercise than did controls.

*

Nijs J, Van Oosterwijk J, Meeus M, Lambrecht L, Metzger K, Frémont M, Paul L. Unravelling the nature of postexertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: the role of elastase, complement C4a and interleukin-1beta. *J Intern Med*. 2010 Apr;267(4):418-35. PMID: 20433584

Following exercise, complement C4a levels go up more in CFS patients than in healthy people.

*

Maes M, Twisk FN. Chronic fatigue syndrome: Harvey and Wessely's (bio)psychosocial model versus a bio(psychosocial) model based on inflammatory and oxidative and nitrosative stress pathways. *BMC Med*. 2010 Jun 15;8:35. PMID: 20550693

The authors describe how physiological abnormalities related to inflammatory, immune, oxidative and nitrosative pathways interfere with exercise tolerance in CFS.

*

Jones DE, Hollingsworth KG, Taylor R, Blamire AM, Newton JL. Abnormalities in pH handling by peripheral muscle and potential regulation by the autonomic nervous system in chronic fatigue syndrome. *J Intern Med*. 2010 Apr;267(4):394-401. PMID: 20433583

CFS patients displayed abnormalities in recovery of intramuscular pH, related to autonomic dysfunction, following exercise.

*

White AT, Light AR, Hughen RW, Bateman L, Martins TB, Hill HR, Light KC. Severity of symptom flare after moderate exercise is linked to cytokine activity in chronic fatigue syndrome. *Psychophysiology*. 2010 Mar 4. PMID: 20230500

CFS patients often display negative responses to exercise, as a result of abnormal inflammatory cytokine activity.

*

Robinson M, Gray SR, Watson MS, Kennedy G, Hill A, Belch JJ, Nimmo MA. Plasma IL-6, its soluble receptors and F2-isoprostanes at rest and during exercise in chronic fatigue syndrome. *Scand J Med Sci Sports*. 2010 Apr;20(2):282-90. PMID: 19422646

CFS patients have higher levels of F(2)-isoprostanes, an indicator of oxidative stress, after exercise.

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Van Oosterwijck J, Nijs J, Meeus M, Lefever I, Huybrechts L, Lambrecht L, Paul L. Pain inhibition and postexertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: an experimental study. *J Intern Med.* 2010 Sep;268(3):265-78. PMID: 20412374

Healthy subjects are able to tolerate a higher level of pain following exercise, while CFS patients are able to tolerate a lower level of pain following exercise.

*

Brown M, Khorana N, Jason LA. The role of changes in activity as a function of perceived available and expended energy in nonpharmacological treatment outcomes for ME/CFS. *J Clin Psychol.* 2010 Oct 25. PMID: 20976708

CFS patients who were within their energy envelope before treatment showed more improvement in physical functioning and fatigue compared with those outside of their energy envelope.

*

VanNess JM, Stevens SR, Bateman L, Stiles TL, Snell CR. Postexertional malaise in women with chronic fatigue syndrome. *J Womens Health (Larchmt).* 2010 Feb;19(2):239-44. PMID: 20095909

Following an exercise test, all the normal sedentary controls recovered quickly (within 24- 48 hours) while none of the CFS patients did. Symptoms the patients reported after the test included fatigue, light-headedness, muscular/joint pain, cognitive dysfunction, headache, nausea, physical weakness, trembling/instability, insomnia and sore throat/glands.

*

Light AR, White AT, Hughen RW, Light KC. Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects. *J Pain.* 2009 Oct;10(10):1099-112. PMID: 19647494

After sustained moderate exercise, CFS patients showed greater increases than control subjects in gene expression for metabolite detecting receptors ASIC3, P2X4, and P2X5, for SNS receptors alpha-2A, beta-1, beta-2, and COMT and IS genes for IL10 and TLR4. This correlated with an exacerbation in their symptoms.

*

Twisk FN, Maes M. A review on cognitive behavioral therapy (CBT) and graded exercise therapy (GET) in myalgic encephalomyelitis (ME) / chronic fatigue syndrome (CFS):

CBT/GET is not only ineffective and not evidence-based, but also potentially harmful for many patients with ME/CFS. *Neuro Endocrinol Lett.* 2009;30(3):284-99. PMID: 19855350

The authors discuss how the use of exercise therapy in CFS may be harmful to patients.

*

Maes M. Inflammatory and oxidative and nitrosative stress pathways underpinning chronic fatigue, somatization and psychosomatic symptoms. *Curr Opin Psychiatry.* 2009 Jan;22(1):75-83. PMID: 19127706

The authors review recent findings on inflammatory and oxidative and nitrosative stress (IO&NS) pathways

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in CFS and suggest that for these patients, exercise can be a trigger factor causing damage.

*

Sorensen B, Jones JF, Vernon SD, Rajeevan MS. Transcriptional control of complement activation in an exercise model of chronic fatigue syndrome. *Mol Med.* 2009 Jan- Feb;15(1-2):34-42. PMID: 19015737

Mannan-binding lectin serine protease 2 (MASP2) was higher than normal following exercise in CFS patients, and this seems related to the phenomenon of post-exertional malaise.

*

Jammes Y, Steinberg JG, Delliaux S, Brégeon F. Chronic fatigue syndrome combines increased exercise-induced oxidative stress and reduced cytokine and Hsp responses. *J Intern Med.* 2009 Aug;266(2):196-206. PMID: 19457057

CFS patients have more severe and longer oxidative stress following exercise, and this may result from delayed and insufficient heat shock proteins protecting the cells.

*

Paul L, Rafferty D, Marshal R. Physiological cost of walking in those with chronic fatigue syndrome (CFS): a case-control study. *Disabil Rehabil.* 2009;31(19):1598-604. PMID: 19848558

Compared to controls walking at the same speed, CFS patients had a lower gross and net oxygen uptake and suffered a higher physiological cost.

Maes M, Twisk FN. Chronic fatigue syndrome: la bête noire of the Belgian health care system. *Neuro Endocrinol Lett.* 2009;30(3):300-11. PMID: 19855351

In case reports, the authors show that Belgian patients who received Graded Exercise Therapy in fact suffered from disorders of the inflammatory/oxidative/nitrosative stress pathways, including intracellular inflammation, an increased translocation of gram-negative enterobacteria (leaky gut), autoimmune reactions and damage by O&NS. They suggest that exercise was inappropriate treatment and recommend policy changes.

*

Jason L, Benton M, Torres-Harding S, Muldowney K. The impact of energy modulation on physical functioning and fatigue severity among patients with ME/CFS. *Patient Educ Couns.* 2009 Nov;77(2):237-41. PMID: 19356884

CFS patients who were able to keep their expended energy close to available energy (i.e. were able to stay within their "energy envelope") experienced significant improvements in physical functioning and fatigue severity.

*

Weinstein AA, Drinkard BM, Diao G, Furst G, Dale JK, Straus SE, Gerber LH. Exploratory analysis of the relationships between aerobic capacity and self-reported fatigue in patients with rheumatoid arthritis, polymyositis, and chronic fatigue syndrome. *PM R.* 2009 Jul;1(7):620-8. PMID: 19627955

Patients with CFS have significantly decreased aerobic capacity. Self-reports of physical activity predicted VO(2peak), and may be used as an indicator of activity-based aerobic capacity. Self-reports of fatigue,

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however, did not correlate with VO₂(peak) and hence are assessing something other than an index of aerobic capacity.

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Thambirajah AA, Sleigh K, Stiver HG, Chow AW. Differential heat shock protein responses to strenuous standardized exercise in chronic fatigue syndrome patients and matched healthy controls. *Clin Invest Med*. 2008 Dec 1;31(6):E319-27. PMID: 19032901

Heat shock protein expression following exercise is abnormal in CFS, suggesting an abnormal response to oxidative stress. This has potential of serving as a biomarker.

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Patrick Neary J, Roberts AD, Leavins N, Harrison MF, Croll JC, Sexsmith JR. Prefrontal cortex oxygenation during incremental exercise in chronic fatigue syndrome. *Clin Physiol Funct Imaging*. 2008 Nov;28(6):364-72. PMID: 18671793

Decreased cerebral oxygenation and blood flow may make contribute to the reduced exercise abilities in CFS.

*

Nijs J, Almond F, De Becker P, Truijien S, Paul L. Can exercise limits prevent post-exertional malaise in chronic fatigue syndrome? An uncontrolled clinical trial. *Clin Rehabil*. 2008 May;22(5):426-35. PMID: 18441039

Limiting both the intensity and duration of exercise prevents important health status changes following a walking exercise in people with CFS, but was unable to prevent short-term symptom increases.

*

Nijs J, Zwinnen K, Meeusen R, de Geus B, De Meirleir K. Comparison of two exercise testing protocols in patients with chronic fatigue syndrome. *J Rehabil Res Dev*. 2007;44(4):553-9. PMID: 18247252

CFS patients engaging in a stepwise exercise protocol had lower mechanical efficiency (ratio peak workload/peak oxygen uptake) than those engaging in a linear exercise protocol.

*

Nijs J, Demol S, Wallman K. Can submaximal exercise variables predict peak exercise performance in women with chronic fatigue syndrome? *Arch Med Res*. 2007 Apr;38(3):350-3. PMID: 17350488

This study aimed at examining whether physiological exercise variables at the submaximal level, defined as 75% of the age-predicted target heart rate, are able to predict peak exercise performance in women with chronic fatigue syndrome (CFS).

*

Yoshiuchi K, Cook DB, Ohashi K, Kumano H, Kuboki T, Yamamoto Y, Natelson BH. A real-time assessment of the effect of exercise in chronic fatigue syndrome. *Physiol Behav*. 2007 Dec 5;92(5):963-8. PMID: 17655887

CFS patients experienced increased physical symptoms after exercise, on average with a five-day delay. Psychological symptoms and cognitive functioning did not change after exercise.

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Nijs J, Meeus M, De Meirleir K. Chronic musculoskeletal pain in chronic fatigue syndrome: recent developments and therapeutic implications. *Man Ther.* 2006 Aug;11(3):187-91. PMID: 16781183

CFS sufferers respond to incremental exercise with a lengthened and accentuated oxidative stress response, explaining muscle pain, postexertional malaise, and the decrease in pain threshold following graded exercise in CFS patients.

*

Cook DB, Nagelkirk PR, Poluri A, Mores J, Natelson BH. The influence of aerobic fitness and fibromyalgia on cardiorespiratory and perceptual responses to exercise in patients with chronic fatigue syndrome. *Arthritis Rheum.* 2006 Oct;54(10):3351-62. PMID: 17009309

In the overall sample, there were no significant differences in cardiorespiratory parameters between the CFS only group and the controls. However, the CFS plus FM group exhibited lower ventilation, lower end-tidal CO₂, and higher ventilatory equivalent of carbon dioxide compared with controls, and slower increases in heart rate compared with both patients with CFS only and controls. Peak oxygen consumption, ventilation, and workload were lower in the CFS plus FM group. Subjects in both the CFS only group and the CFS plus FM group rated exercise as more effortful than did controls.

*

Nijs J, Meeus M, McGregor NR, Meeusen R, de Schutter G, van Hoof E, de Meirleir K. Chronic fatigue syndrome: exercise performance related to immune dysfunction. *Med Sci Sports Exerc.* 2005 Oct;37(10):1647-54. PMID: 16260962

There appears to be an association between intracellular immune deregulation and exercise performance in patients with CFS.

*

Jammes Y, Steinberg JG, Mambrini O, Brégeon F, Delliaux S. Chronic fatigue syndrome: assessment of increased oxidative stress and altered muscle excitability in response to incremental exercise. *J Intern Med.* 2005 Mar;257(3):299-310. PMID: 15715687

Following exercise, CFS patients have lengthened and accentuated oxidative stress together with marked alterations of the muscle membrane excitability.

*

Nijs J, De Meirleir K. Impairments of the 2-5A synthetase/RNase L pathway in chronic fatigue syndrome. *In Vivo.* 2005 Nov-Dec;19(6):1013-21. PMID: 16277015

The 2'-5' oligoadenylate (2-5 A) synthetase/RNase L pathway in CFS patients appears to be both upregulated and deregulated, and this seems to be related to performance during a graded exercise stress test.

*

Black CD, McCully KK. Time course of exercise induced alterations in daily activity in chronic fatigue syndrome. *Dyn Med.* 2005 Oct 28;4:10. PMID: 16255779

CFS patients who attempt to increase their activity by participating in a daily walking program have a difficult time maintaining that increase over time and usually compensate by reducing other activity.

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Bazelmans E, Bleijenberg G, Voeten MJ, van der Meer JW, Folgering H. Impact of a maximal exercise test on symptoms and activity in chronic fatigue syndrome. *J Psychosom Res.* 2005 Oct;59(4):201-8. PMID: 16223622

After exercise, CFS patients reported fatigue for an additional two days, compared to two hours for matched sedentary controls.

*

Snell CR, Vanness JM, Strayer DR, Stevens SR. Exercise capacity and immune function in male and female patients with chronic fatigue syndrome (CFS). *In Vivo.* 2005 Mar- Apr;19(2):387-90. PMID: 15796202

Abnormal immune activity related to oxidative stress, nitric oxide related toxicity and hyperactivation of Rnase-L is related to exercise intolerance in CFS patients.

*

Whistler T, Jones JF, Unger ER, Vernon SD. Exercise responsive genes measured in peripheral blood of women with chronic fatigue syndrome and matched control subjects. *BMC Physiol.* 2005 Mar 24;5(1):5. PMID: 15790422

Following an exercise challenge, CFS patients differed from controls on a variety of genes, including chromatin and nucleosome assembly, cytoplasmic vesicles, membrane transport and G protein-coupled receptor ontologies. Differences in ion transport and ion channel activity were evident at baseline and exaggerated after exercise.

*

Nijs J, De Meirleir K. Prediction of peak oxygen uptake in patients fulfilling the 1994 CDC criteria for chronic fatigue syndrome. *Clin Rehabil.* 2004 Nov;18(7):785-92. PMID: 15573835

A technique to predict peak oxygen uptake in CFS patients was developed.

*

Whiteside A, Hansen S, Chaudhuri A. Exercise lowers pain threshold in chronic fatigue syndrome. *Pain.* 2004 Jun;109(3):497-9. PMID: 15157711

During exercise, normal people have higher pain thresholds and CFS patients have lower pain thresholds.

*

Nijs J, Vanherberghen K, Duquet W, De Meirleir K. Chronic fatigue syndrome: lack of association between pain-related fear of movement and exercise capacity and disability. *Phys Ther.* 2004 Aug;84(8):696-705. PMID: 15283620

This study shows a lack of correlation between kinesiphobia (fear of movement) and exercise capacity, activity limitations, or participation restrictions, at least in patients with CFS who are experiencing widespread muscle or joint pain.

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Siemionow V, Fang Y, Calabrese L, Sahgal V, Yue GH. Altered central nervous system signal during motor performance in chronic fatigue syndrome. *Clin Neurophysiol.* 2004 Oct;115(10):2372-81. PMID: 15351380

CFS involves altered central nervous system signals in controlling voluntary muscle activities, especially when the activities induce fatigue.

*

McCully KK, Smith S, Rajaei S, Leigh JS Jr, Natelson BH. Muscle metabolism with blood flow restriction in chronic fatigue syndrome. *J Appl Physiol.* 2004 Mar;96(3):871-8. PMID: 14578362

CFS patients have evidence of hyperemic flow and reduced oxygen delivery, but this does not seem to result in disturbed muscle metabolism.

*

Nijs J, De Meirleir K, Wolfs S, Duquet W. Disability evaluation in chronic fatigue syndrome: associations between exercise capacity and activity limitations/participation restrictions. *Clin Rehabil.* 2004 Mar;18(2):139-48. PMID: 15053122

These results suggest a moderate association between exercise capacity and activity limitations/participation restrictions in patients with CFS. The observed correlations lack strength to predict activity limitations/ participation restriction based on exercise capacity parameters.

*

Sorensen B, Streib JE, Strand M, Make B, Giclas PC, Fleshner M, Jones JF. Complement activation in a model of chronic fatigue syndrome. *J Allergy Clin Immunol.* 2003 Aug;112(2):397-403. PMID: 12897748

Exercise challenge induced significant increases of the complement split product C4a, but not C3a or C5a, at 6 hours after exercise only in the CFS group. This has potential of serving as a biomarker.

*

Vanness JM, Snell CR, Strayer DR, Dempsey L 4th, Stevens SR. Subclassifying chronic fatigue syndrome through exercise testing. *Med Sci Sports Exerc.* 2003 Jun;35(6):908- 13. PMID: 12783037

Severely affected CFS patients are more impaired during exercise stress tests in terms of peak systolic blood pressure and peak heart rate.

*

Snell CR, Vanness JM, Strayer DR, Stevens SR. Physical performance and prediction of 2-5A synthetase/RNase L antiviral pathway activity in patients with chronic fatigue syndrome. *In Vivo.* 2002 Mar-Apr;16(2):107-9. PMID: 12073768

Seventy-three CFS patients performed a graded exercise test to voluntary exhaustion. Forty-six patients had elevated RNase L levels. The elevated RNase L group had a lower peak V_{O2} and duration than the normal group, but a higher KPS. Both Rnase L and exercise intolerance have potential as biomarkers for CFS.

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Ohashi K, Yamamoto Y, Natelson BH. Activity rhythm degrades after strenuous exercise in chronic fatigue syndrome. *Physiol Behav.* 2002 Sep;77(1):39-44. PMID: 12213500

CFS patients had an abnormal lengthening ($P < .05$) of mean circadian period (MCP) after exercise that was longer than 24 hours.

*

Farquhar WB, Hunt BE, Taylor JA, Darling SE, Freeman R. Blood volume and its relation to peak $\dot{V}O_2$ consumption and physical activity in patients with chronic fatigue. *Am J Physiol Heart Circ Physiol.* 2002 Jan;282(1):H66-71. PMID: 11748048

CFS patients tend to have low blood volume and low peak oxygen consumption, and this seems to be related to their exercise intolerance.

*

Inbar O, Dlin R, Rotstein A, Whipp BJ. Physiological responses to incremental exercise in patients with chronic fatigue syndrome. *Med Sci Sports Exerc.* 2001 Sep;33(9):1463-70. PMID: 11528333

CFS patients demonstrated significantly lower cardiovascular as well as ventilatory values at peak exercise, compared with the control group.

*

Jason LA, Melrose H, Lerman A, Burroughs V, Lewis K, King CP, Frankenberry EL. Managing chronic fatigue syndrome: overview and case study. *AAOHN J.* 1999 Jan;47(1):17-21. PMID: 10205371

The basic principles of envelope theory are explained. By not overexerting themselves, people with CFS can avoid the setbacks and relapses that commonly occur in response to overexertion while increasing their tolerance to activity.

*

McCully KK, Natelson BH. Impaired oxygen delivery to muscle in chronic fatigue syndrome. *Clin Sci (Lond).* 1999 Nov;97(5):603-8; discussion 611-3. PMID: 10545311

Compared to healthy controls, CFS patients suffered abnormally reduced time constant of oxygen delivery and oxidative metabolism following exercise.

*

Mullis R, Campbell IT, Wearden AJ, Morriss RK, Pearson DJ. Prediction of peak oxygen uptake in chronic fatigue syndrome. *Br J Sports Med.* 1999 Oct;33(5):352-6. PMID: 10522640

Using a simple to administer maximal exercise test on a cycle ergometer, it is possible to predict accurately the $\dot{V}O_{2peak}$ of a patient with CFS from peak work rate alone. This

value can then be used as an aid to setting appropriate exercise intensity for a rehabilitation programme.

*

Paul L, Wood L, Behan WM, Maclaren WM. Demonstration of delayed recovery from fatiguing exercise

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in chronic fatigue syndrome. *Eur J Neurol.* 1999 Jan;6(1):63-9. PMID: 10209352

Throughout a period of exercise, patients were able to exercise less than controls. Recovery was prolonged in the patient group, however, with a significant difference compared to initial amount of exercise being evident during the recovery phase after exercise ($P = 0.001$) and also at 24 h ($P < 0.001$). These findings support the clinical complaint of delayed recovery after exercise in patients with CFS.

*

LaManca JJ, Sisto SA, DeLuca J, Johnson SK, Lange G, Pareja J, Cook S, Natelson BH. Influence of exhaustive treadmill exercise on cognitive functioning in chronic fatigue syndrome. *Am J Med.* 1998 Sep 28;105(3A):59S-65S. PMID: 9790484

After a physically demanding exercise, CFS subjects demonstrated impaired cognitive processing compared with healthy individuals.

*

Blackwood SK, MacHale SM, Power MJ, Goodwin GM, Lawrie SM. Effects of exercise on cognitive and motor function in chronic fatigue syndrome and depression. *J Neurol Neurosurg Psychiatry.* 1998 Oct;65(4):541-6. PMID: 9771781

After exertion, patients with chronic fatigue syndrome showed a greater decrease than healthy controls on everyday tests of focused and sustained attention, as well as greater deterioration than depressed patients on the focused attention task.

*

Lane RJ, Barrett MC, Woodrow D, Moss J, Fletcher R, Archard LC. Muscle fibre characteristics and lactate responses to exercise in chronic fatigue syndrome. *J Neurol Neurosurg Psychiatry.* 1998 Mar;64(3):362-7. PMID: 9527150

Muscle histometry in patients with chronic fatigue syndrome generally did not show the changes expected as a result of inactivity. However, patients with abnormal lactate responses to exercise had a significantly lower proportion of mitochondria rich type 1 muscle fibres.

*

Fischler B, Dendale P, Michiels V, Cluydts R, Kaufman L, De Meirleir K. Physical fatigability and exercise capacity in chronic fatigue syndrome: association with disability, somatization and psychopathology. *J Psychosom Res.* 1997 Apr;42(4):369-78. PMID: 9160276

The authors present evidence against an association in CFS between avoidance of physically demanding tasks and early anaerobic metabolism during effort.

*

Kent-Braun JA, Sharma KR, Weiner MW, Massie B, Miller RG. Central basis of muscle fatigue in chronic fatigue syndrome. *Neurology.* 1993 Jan;43(1):125-31.

Voluntary activation of the tibialis was significantly lower in CFS patients during maximal sustained exercise.

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Wong R, Lopaschuk G, Zhu G, Walker D, Catellier D, Burton D, Teo K, Collins-Nakai R, Montague T. Skeletal muscle metabolism in the chronic fatigue syndrome. In vivo assessment by ³¹P nuclear magnetic resonance spectroscopy. *Chest*. 1992 Dec;102(6):1716-22. PMID: 1446478

CFS patients reach exhaustion much more rapidly than normal subjects, at which point they also have relatively reduced intracellular concentrations of ATP. These data suggest a defect of oxidative metabolism with a resultant acceleration of glycolysis in the working skeletal muscles of CFS patients.

*

Montague TJ, Marrie TJ, Klassen GA, Bewick DJ, Horacek BM. Cardiac function at rest and with exercise in the chronic fatigue syndrome. *Chest*. 1989 Apr;95(4):779-84. PMID: 2924607

Patients with chronic fatigue syndrome have normal resting cardiac function but a markedly abbreviated exercise capacity characterized by slow acceleration of heart rate and fatigue of exercising muscles long before peak heart rate is achieved.

Oxidative Stress and Inflammation

Morris G1, Anderson G, Dean O, Berk M, Galecki P, Martin-Subero M, Maes M. The Glutathione System: A New Drug Target in Neuroimmune Disorders. *Mol Neurobiol*. 2014 Apr 22. PMID: 24752591

Glutathione depletion and concomitant increase in oxidative and nitrosative stress pathways as well as mitochondrial dysfunctions play a role in the pathophysiology of diverse neuroimmune disorders, including depression, myalgic encephalomyelitis/chronic fatigue syndrome and Parkinson's disease, suggesting that depleted GSH is an integral part of these diseases.

*

Morris G, Maes M. Oxidative and Nitrosative Stress and Immune-Inflammatory Pathways in Patients with Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS). *Curr Neuropharmacol*. 2014 Mar;12(2):168-85. PMID: 24669210

Sources of continuous activation of O&NS and immune-inflammatory pathways in ME/CFS are chronic, intermittent and opportunistic infections, bacterial translocation, autoimmune responses, mitochondrial dysfunctions, activation of the Toll-Like Receptor Radical Cycle, and decreased antioxidant levels. Consequences of chronically activated O&NS and immune-inflammatory pathways in ME/CFS are brain disorders, including neuroinflammation and brain hypometabolism / hypoperfusion, toxic effects of nitric oxide and peroxynitrite, lipid peroxidation and oxidative damage to DNA, secondary autoimmune responses directed against disrupted lipid membrane components and proteins, mitochondrial dysfunctions with a disruption of energy metabolism (e.g. compromised ATP production) and dysfunctional intracellular signaling pathways.

*

Morris G, Berk M, Galecki P, Maes M. The Emerging Role of Autoimmunity in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). *Mol Neurobiol*. 2013 Sep 26. PMID: 24068616

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Abnormalities in ME/CFS include elevated oxidative and nitrosative stress (O&NS), activation of immunoinflammatory pathways, and mitochondrial dysfunctions with depleted levels of adenosine triphosphate (ATP) synthesis. There is also evidence that many patients with ME/CFS (up to around 60%) may suffer from autoimmune responses. This paper reviews the potential sources of the autoimmunity.

*

Castro-Marrero J, Cordero MD, Saez-Francas N, Jimenez-Gutiérrez C, Aguilar-Montilla FJ, Aliste L, Alegre-Martin J. Could mitochondrial dysfunction be a differentiating marker between Chronic Fatigue Syndrome and Fibromyalgia? *Antioxid Redox Signal*. 2013 Apr 22. PMID: 23600892

Peripheral blood mononuclear cells (PBMC) showed decreased levels of CoQ10 and ATP from CFS and FM subjects compared to controls. CFS/FM patients had significantly increased levels of lipid peroxidation, indicative of oxidative stress-induced damage.

Mitochondrial citrate synthase activity, mitochondrial DNA content (mtDNA/gDNA ratio) and expression levels of PGC-1 α and TFAM were significantly lower in FM patients than in controls.

*

Broderick G, Katz BZ, Fernandes H, Fletcher MA, Klimas N, Smith FA, O'Gorman MR, Vernon SD, Taylor R. Cytokine expression profiles of immune imbalance in post-mononucleosis chronic fatigue. *J Transl Med*. 2012 Sep 13;10:191. PMID: 22973830

Researchers measured the concentrations of IL-1a, 1b, 2, 4, 5, 6, 8, 10, 12 (p70), 13, 15, 17 and 23, IFN- γ , TNF- α and TNF- β in CFS patients vs. controls. Study results suggest that co-expression patterns in as few as 5 cytokines associated with Th17 function may hold promise as a tool for the diagnosis of post-infectious CFS.

*

Zhang HY, Liu ZD, Hu CJ, Wang DX, Zhang YB, Li YZ. Up-regulation of TGF- β 1 mRNA expression in peripheral blood mononuclear cells of patients with chronic fatigue syndrome. *J Formos Med Assoc*. 2011 Nov;110(11):701-4. PMID: 22118314

The expression of TGF- β 1 in PBMCs is significantly elevated in patients with CFS.

*

Maes M, Twisk FN, Kubera M, Ringel K. Evidence for inflammation and activation of cell-mediated immunity in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): Increased interleukin-1, tumor necrosis factor- α , PMN-elastase, lysozyme and neopterin. *J Affect Disord*. 2011 Oct 3. PMID: 21975140

The findings show that ME/CFS is characterized by low-grade inflammation and activation of cell-mediated immunity and suggest that inflammatory mediators such as IL-1 and TNF α are factors in the disease.

*

Maes M, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E. Increased plasma peroxides as a marker of oxidative stress in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *Med Sci Monit*. 2011 Apr;17(4):SC11-5. PMID: 21455120

Plasma peroxide concentrations were significantly higher in patients with ME/CFS than in normal controls. There was a trend towards significantly higher serum oxLDL antibodies in ME/CFS than in

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controls. Both biomarkers contributed significantly in discriminating between patients with ME/CFS and normal controls. Plasma peroxide and serum oxLDL antibody levels were both significantly related to one of the FF symptoms. The results show that ME/CFS is characterized by increased oxidative stress.

*

Brkic S, Tomic S, Maric D, Novakov Mikic A, Turkulov V. Lipid peroxidation is elevated in female patients with chronic fatigue syndrome. *Med Sci Monit.* 2010 Nov 30;16(12):CR628-32. PMID: 21119582

CFS is associated with lipid peroxidation and oxidative stress. High levels of malondialdehyde, positively correlated with total cholesterol and lower HDL cholesterol levels, might be indicative of proatherogenic events in female CFS patients.

*

Kennedy G, Khan F, Hill A, Underwood C, Belch JJ. Biochemical and vascular aspects of pediatric chronic fatigue syndrome. *Arch Pediatr Adolesc Med.* 2010 Sep;164(9):817-23. PMID: 20819963

Biomedical anomalies seen in adults with CFS/ME-increased oxidative stress and increased white blood cell apoptosis-can also be observed in children with clinically diagnosed CFS/ME compared with matched controls.

*

Miwa K, Fujita M. Fluctuation of serum vitamin E (alpha-tocopherol) concentrations during exacerbation and remission phases in patients with chronic fatigue syndrome. *Heart Vessels.* 2010 Jul;25(4):319-23. PMID: 20676841

CFS patients have lower levels of Vitamin E (and therefore possible greater oxidative stress) during times of exacerbation than during times of remission.

*

Jason LA, Porter N, Herrington J, Sorenson M, Kubow S. Kindling and Oxidative Stress as Contributors to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *J Behav Neurosci Res.* 2009 Jan 1;7(2):1-17. PMID: 21253446

CFS can affect the immune, neuroendocrine, autonomic, and neurologic systems. Abnormal biological findings among some patients have included aberrant ion transport and ion channel activity, cortisol deficiency, sympathetic nervous system hyperactivity, EEG spike waves, left ventricular dysfunction in the heart, low natural killer cell cytotoxicity, and a shift from Th1 to Th2 cytokines. We propose that the kindling and oxidative stress theories provide a heuristic template for better understanding of this illness.

*

Maes M, Twisk FN. Why myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) may kill you: disorders in the inflammatory and oxidative and nitrosative stress (IO&NS) pathways may explain cardiovascular disorders in ME/CFS. *Neuro Endocrinol Lett.* 2009;30(6):677-93. PMID: 20038921

Previous reports suggest that CFS patients dying of heart failure do so at a significantly lower age than non-patients (59 years vs. 83 years). A number of abnormalities in CFS may be responsible for this, including: a) chronic low grade inflammation with extended production of nuclear factor kappa B and COX-

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2 and increased levels of tumour necrosis factor alpha; b) increased O&NS with increased peroxide levels, and phospholipid oxidation including oxidative damage to phosphatidylinositol; c) decreased levels of specific antioxidants, i.e. coenzyme Q10, zinc and dehydroepiandrosterone-sulphate; d) bacterial translocation as a result of leaky gut; e) decreased omega-3 polyunsaturated fatty acids (PUFAs), and increased omega-6 PUFA and saturated fatty acid levels; and f) the presence of viral and bacterial infections and psychological stressors.

*

Miwa K, Fujita M. Increased oxidative stress suggested by low serum vitamin E concentrations in patients with chronic fatigue syndrome. *Int J Cardiol.* 2009 Aug 14;136(2):238-9. PMID: 18684522

Patients with CFS have lower serum alpha-tocopherol concentrations, suggesting the presence of oxidative stress in the illness.

*

Spence VA, Kennedy G, Belch JJ, Hill A, Khan F. Low-grade inflammation and arterial wave reflection in patients with chronic fatigue syndrome. *Clin Sci (Lond).* 2008 Apr;114(8):561-6. PMID: 18031285

Measures related to oxidative stress were studied in CFS patients.

*

Fulle S, Pietrangelo T, Mancinelli R, Saggini R, Fanò G. Specific correlations between muscle oxidative stress and chronic fatigue syndrome: a working hypothesis. *J Muscle Res Cell Motil.* 2007;28(6):355-62. PMID: 18274865

The role of oxidative stress in CFS is an emerging focus of research due to evidence of its association with some pathological features of this syndrome. New data collectively support the presence of specific critical points in the muscle that are affected by free radicals.

*

Pall ML, Bedient SA. The NO/ONOO- cycle as the etiological mechanism of tinnitus. *Int Tinnitus J.* 2007;13(2):99-104. PMID: 18229788

Tinnitus may be related to abnormal levels of such cycle elements as N-methyl-D- aspartate activity; oxidative stress; nitric oxide; peroxynitrite; vanilloid activity; NF-kappaB activity; and intracellular calcium levels.

*

Richards RS, Wang L, Jelinek H. Erythrocyte oxidative damage in chronic fatigue syndrome. *Arch Med Res.* 2007 Jan;38(1):94-8. PMID: 17174731

CFS patients showed oxidative stress evidence in terms of misshapen red blood cells and levels of malondialdehyde (MDA), methemoglobin (metHb) and 2,3- diphosphoglyceric acid (2,3-DPG).

*

Maes M, Mihaylova I, Leunis JC. Chronic fatigue syndrome is accompanied by an IgM- related immune response directed against neopitopes formed by oxidative or nitrosative damage to lipids and proteins. *Neuro Endocrinol Lett.* 2006 Oct;27(5):615-21. PMID: 17159817

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CFS is characterized by an IgM-related immune response directed against disrupted lipid membrane components, by-products of lipid peroxidation, S-farnesyl-L-cysteine, and NO- modified amino-acids, which are normally not detected by the immune system but due to oxidative and nitrosative damage have become immunogenic.

*

Maes M, Mihaylova I, De Ruyter M. Lower serum zinc in Chronic Fatigue Syndrome (CFS): relationships to immune dysfunctions and relevance for the oxidative stress status in CFS. *J Affect Disord.* 2006 Feb;90(2-3):141-7. PMID: 16338007

CFS is accompanied by a low serum zinc status and that the latter is related to signs of inflammation and defects in early T cell activation pathways. Since zinc is a strong anti-oxidant, the present results further support the findings that CFS is accompanied by increased oxidative stress.

*

Kennedy G, Spence VA, McLaren M, Hill A, Underwood C, Belch JJ. Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms. *Free Radic Biol Med.* 2005 Sep 1;39(5):584-9. PMID: 16085177

CFS patients showed elevations in a variety of measures, including isoprostanes, of oxidative stress.

*

Pall ML. Nitric oxide and the etiology of chronic fatigue syndrome: giving credit where credit is due. *Med Hypotheses.* 2005;65(3):631-3.

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Nijs J, Van de Velde B, De Meirleir K. Pain in patients with chronic fatigue syndrome: does nitric oxide trigger central sensitisation? *Med Hypotheses.* 2005;64(3):558-62. PMID: 15617866

It is hypothesised that a nitric oxide (NO)-dependent reduction in inhibitory activity of the central nervous system and consequent central sensitisation accounts for chronic widespread pain in CFS patients.

*

Chaudhuri A, Behan PO. In vivo magnetic resonance spectroscopy in chronic fatigue syndrome. *Prostaglandins Leukot Essent Fatty Acids.* 2004 Sep;71(3):181-3. PMID: 15253888

Cell membrane oxidative stress may offer a common explanation for the observed MRS changes in the muscles and brain of CFS patients and this may have important therapeutic implications.

*

Smirnova IV, Pall ML. Elevated levels of protein carbonyls in sera of chronic fatigue syndrome patients. *Mol Cell Biochem.* 2003 Jun;248(1-2):93-5. PMID: 12870659

Elevated protein carbonyl levels confirm earlier reports suggesting that oxidative stress is associated with CFS and are consistent with a prediction of the elevated nitric oxide/peroxynitrite theory of chronic fatigue syndrome and related conditions.

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Vecchiet J, Cipollone F, Falasca K, Mezzetti A, Pizzigallo E, Bucciarelli T, De Laurentis S, Affaitati G, De Cesare D, Giamberardino MA. Relationship between musculoskeletal symptoms and blood markers of oxidative stress in patients with chronic fatigue syndrome. *Neurosci Lett*. 2003 Jan 2;335(3):151-4. PMID: 12531455

Increased oxidative stress and decreased antioxidant defenses are related to the extent of symptomatology in CFS.

*

Manuel y Keenoy B, Moorkens G, Vertommen J, De Leeuw I. Antioxidant status and lipoprotein peroxidation in chronic fatigue syndrome. *Life Sci*. 2001 Mar 16;68(17):2037-49. PMID: 11388705

Patients with CFS have increased susceptibility of LDL and VLDL to copper-induced peroxidation, and this is related both to their lower levels of serum transferrin and to other unidentified pro-oxidising effects of CFS.

*

Pall ML. Common etiology of posttraumatic stress disorder, fibromyalgia, chronic fatigue syndrome and multiple chemical sensitivity via elevated nitric oxide/peroxynitrite. *Med Hypotheses*. 2001 Aug;57(2):139-45. PMID: 11461161

Evidence supporting the role of elevated nitric oxide/peroxynitrite in CFS and other disease states is summarized

*

Richards RS, Roberts TK, Dunstan RH, McGregor NR, Butt HL. Free radicals in chronic fatigue syndrome: cause or effect? *Redox Rep*. 2000;5(2-3):146-7. PMID: 10939298

Free radicals may be a problem in CFS.

*

Fulle S, Mecocci P, Fanó G, Vecchiet I, Vecchini A, Racciotti D, Cherubini A, Pizzigallo E, Vecchiet L, Senin U, Beal MF. Specific oxidative alterations in vastus lateralis muscle of patients with the diagnosis of chronic fatigue syndrome. *Free Radic Biol Med*. 2000 Dec 15;29(12):1252-9. PMID: 11118815

The authors detected oxidative damage to DNA and lipids in muscle specimens of CFS patients as compared to age-matched controls, as well as increased activity of the antioxidant enzymes catalase, glutathione peroxidase, and transferase, and increases in total glutathione plasma levels.

*

Richards RS, Roberts TK, McGregor NR, Dunstan RH, Butt HL. Blood parameters indicative of oxidative stress are associated with symptom expression in chronic fatigue syndrome. *Redox Rep*. 2000;5(1):35-41. PMID: 10905542

CFS patients had increases in malondialdehyde, methaemoglobin, mean erythrocyte volume and 2,3-diphosphoglycerate compared with controls. Methaemoglobin was found to be the major component

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associated with variation in symptom expression, including fatigue, musculoskeletal symptoms, pain and sleep disturbance. Variation in levels of malondialdehyde and 2,3-diphosphoglycerate were associated with variations in cognitive symptoms and sleep disturbance. These data suggest that oxidative stress due to excess free radical formation is a contributor to the pathology of CFS and was associated with symptom presentation.

*

Pall ML. Elevated, sustained peroxynitrite levels as the cause of chronic fatigue syndrome. *Med Hypotheses*. 2000 Jan;54(1):115-25. PMID: 10790736

The author proposes a hypothesis of CFS in which either viral or bacterial infection induces one or more cytokines, IL-1beta IL-6, TNF-alpha and IFN-gamma. These induce nitric oxide synthase (iNOS), leading to increased nitric oxide levels. Nitric oxide, in turn, reacts with superoxide radical to generate the potent oxidant peroxynitrite. Multiple amplification and positive feedback mechanisms are proposed by which once peroxynitrite levels are elevated, they tend to be sustained at a high level.

Cytokines & Complement

Nakamura T, Schwander S, Donnelly R, Cook DB, Ortega F, Togo F, Yamamoto Y, Cherniack NS, Klapholz M, Rapoport D, Natelson BH. Exercise and sleep deprivation do not change cytokine expression levels in patients with chronic fatigue syndrome. *Clin Vaccine Immunol*. 2013 Nov;20(11):1736-42. PMID: 24027260

The authors conducted repeat blood sampling for cytokine levels from healthy subjects and CFS patients during both postexercise and total sleep deprivation nights and assayed for protein levels in the blood samples, mRNA activity in peripheral blood lymphocytes (PBLs), and function in resting and stimulated PBLs. They found that these environmental manipulations did not produce clinically significant upregulation of proinflammatory cytokines.

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Stringer EA, Baker KS, Carroll IR, Montoya JG, Chu L, Maecker HT, Younger JW. Daily cytokine fluctuations, driven by leptin, are associated with fatigue severity in chronic fatigue syndrome: evidence of inflammatory pathology. *J Transl Med*. 2013 Apr 9;11:93. PMID: 23570606

Self-reported fatigue severity was significantly correlated with leptin levels in 60% of the participants with CFS and in 10% of healthy controls. A machine learning algorithm distinguished high from low fatigue days in the CFS group with 78.3% accuracy.

*

Smylie AL, Broderick G, Fernandes H, Razdan S, Barnes Z, Collado F, Sol C, Fletcher MA, Klimas N. A comparison of sex-specific immune signatures in Gulf War illness and chronic fatigue syndrome. *BMC Immunol*. 2013 Jun 25;14:29. PMID: 23800166

Common to both Gulf War Illness and CFS, IL-10 and IL-23 expression contributed in an illness and time-dependent manner, accompanied in male subjects by NK and Th1 markers IL-12, IL-15, IL-2 and IFN γ . In female GWI and CFS subjects IL-10 was again identified as a delineator but this time in the context of IL-17 and Th2 markers IL-4 and IL-5. Exercise response also differed between sexes: male GWI subjects presented characteristic cytokine signatures at rest but not at peak effort whereas the opposite was true

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for female subjects.

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Nakamura T, Schwander SK, Donnelly R, Ortega F, Togo F, Broderick G, Yamamoto Y, Cherniack NS, Rapoport D, Natelson BH. Cytokines across the night in chronic fatigue syndrome with and without fibromyalgia. *Clin Vaccine Immunol.* 2010 Apr;17(4):582-7. PMID: 20181767

The authors found evidence to support a role for an increase in interleukin-10, an anti-inflammatory cytokine. Although the changes were small, they may contribute to the common complaint in CFS patients of disrupted sleep.

*

Broderick G, Fuite J, Kreitz A, Vernon SD, Klimas N, Fletcher MA. A formal analysis of cytokine networks in Chronic Fatigue Syndrome. *Brain Behav Immun.* 2010 May 4. PMID: 20447453

CFS patients have specific immune responses related to the presence of inflammatory processes consistent with the presence of a latent viral infection.

*

Fletcher MA, Zeng XR, Barnes Z, Levis S, Klimas NG. Plasma cytokines in women with chronic fatigue syndrome. *J Transl Med.* 2009 Nov 12;7:96. PMID: 19909538

CFS patients display a large number of abnormal cytokines, with increases in some (LTalpha, IL-1alpha, IL-1beta, IL-4, IL-5, IL-6 and IL-12) and decreases in others (IL-8,

IL-13 and IL-15). Some of these have the potential of serving as biomarkers for the disease.

*

Geller RD, Giclas PC. Chronic fatigue syndrome and complement activation. *BMJ Case Rep.* 2009;2009. PMID: 21686614

This report describes a case of chronic fatigue syndrome (CFS) that followed a well-documented episode of acute Epstein-Barr virus (EBV) mononucleosis. After 2 years of chronic fatigue following the acute illness, measurements of complement split products were positive for complement activation and remained positive for 14 months, after which the patient then recovered from CFS.

*

Nater UM, Youngblood LS, Jones JF, Unger ER, Miller AH, Reeves WC, Heim C. Alterations in diurnal salivary cortisol rhythm in a population-based sample of cases with chronic fatigue syndrome. *Psychosom Med.* 2008 Apr;70(3):298-305. PMID: 18378875

The study results suggest an altered diurnal cortisol rhythm and IL-6 concentrations in CFS cases.

*

Metzger K, Frémont M, Roelant C, De Meirleir K. Lower frequency of IL-17F sequence variant (His161Arg) in chronic fatigue syndrome patients. *Biochem Biophys Res Commun.* 2008 Nov 7;376(1):231-3. PMID: 18774769

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T helper 17 (Th17) cells belong to a recently identified subset of T helper cells, with crucial regulatory function in inflammatory and autoimmune processes. Th17 cells are implicated in allergic inflammation, intestinal diseases, central nervous system inflammation, disorders that may all contribute to the pathophysiology of CFS. IL-17F is one of the pro-inflammatory cytokines secreted by Th17 cells. The results suggest a role of Th17 cells in the pathogenesis of CFS.

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Vollmer-Conna U, Cameron B, Hadzi-Pavlovic D, Singletary K, Davenport T, Vernon S, Reeves WC, Hickie I, Wakefield D, Lloyd AR; Dubbo Infective Outcomes Study Group. Postinfective fatigue syndrome is not associated with altered cytokine production. *Clin Infect Dis*. 2007 Sep 15;45(6):732-5. PMID: 17712757

The authors concluded that ongoing production of cytokines does not play a role in postinfective fatigue syndrome.

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ter Wolbeek M, van Doornen LJ, Kavelaars A, van de Putte EM, Schedlowski M, Heijnen CJ. Longitudinal analysis of pro- and anti-inflammatory cytokine production in severely fatigued adolescents. *Brain Behav Immun*. 2007 Nov;21(8):1063-74. PMID: 17544255

Although overlap in symptomatology between the general population and patients with CFS was observed, only CFS patients show a skewing of the cytokine balance towards an anti-inflammatory profile.

*

Pall ML. Nitric oxide synthase partial uncoupling as a key switching mechanism for the NO/ONOO- cycle. *Med Hypotheses*. 2007;69(4):821-5. PMID: 17448611

The author discusses how NF-kappa-beta activity in CFS might be triggered.

*

Carlo-Stella N, Badulli C, De Silvestri A, Bazzichi L, Martinetti M, Lorusso L, Bombardieri S, Salvaneschi L, Cuccia M. A first study of cytokine genomic polymorphisms in CFS: Positive association of TNF-857 and IFNgamma 874 rare alleles. *Clin Exp Rheumatol*. 2006 Mar-Apr;24(2):179-82. PMID: 16762155

There is a highly significant increase of TNF -857 TT and CT genotypes among CFS patients with respect to controls and a significant decrease of IFN gamma low producers (A/A) among patients with respect to controls.

*

Gaab J, Rohleder N, Heitz V, Engert V, Schad T, Schürmeyer TH, Ehlert U. Stress-induced changes in LPS-induced pro-inflammatory cytokine production in chronic fatigue syndrome. *Psychoneuroendocrinology*. 2005 Feb;30(2):188-98. PMID: 15471616

Although cortisol responses to stress were normal, pro-inflammatory cytokine levels in CFS patients were significantly attenuated. TNF-alpha and IL-6 were especially problematic.

*

Tomoda A, Judoï T, Rabab el-M, Matsumoto T, Park TH, Miike T. Cytokine production and modulation: comparison of patients with chronic fatigue syndrome and normal controls. *Psychiatry Res*. 2005 Mar

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30;134(1):101-4. PMID: 15808295

CFS patients showed significantly lower mRNA levels and transforming growth factor- beta1 (TGF-beta1) production. Cytokine dysregulation affects CFS pathogenesis. TGF- beta1 may aid treatment because it affects CFS inflammatory characteristics.

*

Sackner MA, Gummels EM, Adams JA. Say NO to fibromyalgia and chronic fatigue syndrome: an alternative and complementary therapy to aerobic exercise. *Med Hypotheses*. 2004;63(1):118-23. PMID: 15193362

It is hypothesized that CFS has chronic inflammation at its basis.

*

Skowera A, Cleare A, Blair D, Bevis L, Wessely SC, Peakman M. High levels of type 2 cytokine-producing cells in chronic fatigue syndrome. *Clin Exp Immunol*. 2004 Feb;135(2):294-302. PMID: 14738459

The authors found evidence of a significant bias towards Th2- and Tc2-type immune responses in CFS compared to controls. In contrast, levels of IFN-gamma, IL-2 and IL- 10-producing cells were similar in both study groups. There is an effector memory cell bias towards type 2 responsiveness in patients with CFS, as well as ongoing type 0 immune activation in unstimulated cultures of peripheral blood cells.

*

Shephard RJ. Cytokine responses to physical activity, with particular reference to IL-6: sources, actions, and clinical implications. *Crit Rev Immunol*. 2002;22(3):165-82. PMID: 12498381

Prolonged endurance exercise induces a sequenced release of pro- and anti- inflammatory cytokines, and IL-6 plays a dominant role. Although many types of cells are capable of producing cytokines, the main source of the exercise-induced IL-6 production appears to be the exercising muscle.

*

Arnold MC, Papanicolaou DA, O'Grady JA, Lotsikas A, Dale JK, Straus SE, Grafman J. Using an interleukin-6 challenge to evaluate neuropsychological performance in chronic fatigue syndrome. *Psychol Med*. 2002 Aug;32(6):1075-89. PMID: 12214788

An IL-6 provocation exacerbated the CFS patients' self-reported symptoms but did not reveal notable cognitive impairments between patients and controls during cytokine- induced acute influenza-like symptoms.

*

Kerr JR, Barah F, Matthey DL, Laing I, Hopkins SJ, Hutchinson IV, Tyrrell DA. Circulating tumour necrosis factor-alpha and interferon-gamma are detectable during acute and convalescent parvovirus B19 infection and are associated with prolonged and chronic fatigue. *J Gen Virol*. 2001 Dec;82(Pt 12):3011-9. PMID: 11714978

Patients with a parvovirus B19 infection had elevated IL-6, TNF-alpha, IL-1 beta, and IFN- gamma.

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Visser J, Graffelman W, Blauw B, Haspels I, Lentjes E, de Kloet ER, Nagelkerken L. LPS- induced IL-10 production in whole blood cultures from chronic fatigue syndrome patients is increased but supersensitive to inhibition by dexamethasone. *J Neuroimmunol.* 2001 Oct 1;119(2):343-9. PMID: 11585638

In CFS patients, LPS-induced cytokine secretion in whole blood cultures showed a significant increase in IL-10 and a trend towards a decrease in IL-12 as compared with healthy controls. In general, the data are suggestive for a disturbed glucocorticoid regulation of IL-10 in CFS.

*

Patarca-Montero R, Antoni M, Fletcher MA, Klimas NG. Cytokine and other immunologic markers in chronic fatigue syndrome and their relation to neuropsychological factors. *Appl Neuropsychol.* 2001;8(1):51-64. PMID: 11388124

In patients with CFS there is chronic lymphocyte overactivation with cytokine abnormalities that include perturbations in plasma levels of proinflammatory cytokines and decrease in the ratio of Type 1 to Type 2 cytokines produced by lymphocytes in vitro following mitogen stimulation.

*

Hanson SJ, Gause W, Natelson B. Detection of immunologically significant factors for chronic fatigue syndrome using neural-network classifiers. *Clin Diagn Lab Immunol.* 2001 May;8(3):658-62. PMID: 11329477

Neural-network classifiers were used to detect immunological differences in groups of chronic fatigue syndrome (CFS) patients that heretofore had not shown significant differences from controls. Of all the cytokines evaluated, the only one to be in the final model was interleukin-4 (IL-4).

*

Cannon JG, Angel JB, Ball RW, Abad LW, Fagioli L, Komaroff AL. Acute phase responses and cytokine secretion in chronic fatigue syndrome. *J Clin Immunol.* 1999 Nov;19(6):414- 21. PMID: 10634215

CFS is associated with increased IL-6 secretion which is manifested by chronically elevated plasma alpha2-macroglobulin concentrations.

*

Moss RB, Mercandetti A, Vojdani A. TNF-alpha and chronic fatigue syndrome. *J Clin Immunol.* 1999 Sep;19(5):314-6. PMID: 10535608

CFS patients have a significant increase serum TNF-alpha in patients with CFS ($P < 0.0001$) compared to non-CFS controls.

*

Gupta S, Aggarwal S, Starr A. Increased production of interleukin-6 by adherent and non- adherent mononuclear cells during 'natural fatigue' but not following 'experimental fatigue' in patients with chronic fatigue syndrome. *Int J Mol Med.* 1999 Feb;3(2):209-13. PMID: 9917531

A significant increase in spontaneous, phytohemagglutinin- and lipopolysaccharide- induced IL-6 secretion by both lymphocytes and monocytes was observed in CFS patients during 'natural fatigue' as compared to during state. However, no such changes in IL-6 production were observed during fatigue experienced after exercise. These data suggest a role of IL-6 in natural symptomatology and perhaps in the

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pathogenesis of CFS. In addition, the data demonstrate that laboratory-induced fatigue (experimental fatigue) may not be a good model to study immunological changes in CFS; immunological parameters should be studied in a longitudinal manner during the natural course of the disease.

*

Bennett AL, Chao CC, Hu S, Buchwald D, Fagioli LR, Schur PH, Peterson PK, Komaroff AL. Elevation of bioactive transforming growth factor-beta in serum from patients with chronic fatigue syndrome. *J Clin Immunol.* 1997 Mar;17(2):160-6. PMID: 9083892

TGF-beta levels were significantly higher in CFS patients compared to patients with various diseases known to be associated with immunologic abnormalities and/or pathologic fatigue.

*

Gupta S, Aggarwal S, See D, Starr A. Cytokine production by adherent and non-adherent mononuclear cells in chronic fatigue syndrome. *J Psychiatr Res.* 1997 Jan-Feb;31(1):149- 56. PMID: 9201656

The levels of spontaneously (unstimulated) produced TNF-alpha by non-adherent lymphocytes and spontaneously produced IL-6 by both adherent monocytes and non-adherent lymphocytes were significantly increased in CFS patients. The abnormality of IL-6 was also observed at mRNA level. In contrast, spontaneously produced IL-10 by both adherent and non-adherent cells and by PHA-activated non-adherent cells were decreased.

*

Peterson PK, Sirm SA, Grammith FC, Schenck CH, Pheley AM, Hu S, Chao CC. Effects of mild exercise on cytokines and cerebral blood flow in chronic fatigue syndrome patients. *Clin Diagn Lab Immunol.* 1994 Mar;1(2):222-6. PMID: 7496949

At rest, serum transforming growth factor beta (TGF-beta) levels were elevated in CFS patients. Serum TGF-beta and cerebral blood flow abnormalities, detected by single-photon emission-computed tomographic scanning, were accentuated postexercise in the CFS group.

*

Patarca R, Klimas NG, Lugtendorf S, Antoni M, Fletcher MA. Dysregulated expression of tumor necrosis factor in chronic fatigue syndrome: interrelations with cellular sources and patterns of soluble immune mediator expression. *Clin Infect Dis.* 1994 Jan;18 Suppl 1:S147-53. PMID: 8148443

CFS patients had higher circulating levels of TNF-alpha and TNF-beta than controls.

*

Chao CC, Janoff EN, Hu SX, Thomas K, Gallagher M, Tsang M, Peterson PK. Altered cytokine release in peripheral blood mononuclear cell cultures from patients with the chronic fatigue syndrome. *Cytokine.* 1991 Jul;3(4):292-8. PMID: 1873478

Serum bioactive transforming growth factor beta (TGF-beta) levels were higher in patients with CFS. Lipopolysaccharide-stimulated release of interleukin 1 beta (IL-1 beta), IL-6, and tumor necrosis factor-alpha was increased; enhanced IL-6 release to phytohemagglutinin was also observed.

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Cheney PR, Dorman SE, Bell DS. Interleukin-2 and the chronic fatigue syndrome. *Ann Intern Med.* 1989 Feb 15;110(4):321. PMID: 2783643

RNase L

Nijs J, Frémont M. Intracellular immune dysfunction in myalgic encephalomyelitis/chronic fatigue syndrome: state of the art and therapeutic implications. *Expert Opin Ther Targets.* 2008 Mar;12(3):281-9. PMID: 18269338

Proteolytic cleavage of the native RNase L enzyme is characteristic of the dysregulation of intracellular immunity in CFS.

*

Bisbal C, Silverman RH. Diverse functions of RNase L and implications in pathology. *Biochimie.* 2007 Jun-Jul;89(6-7):789-98. PMID: 17400356

The role of RNase-L, known to be dysfunctional in CFS, is discussed.

*

Nijs J, De Meirleir K. Impairments of the 2-5A synthetase/RNase L pathway in chronic fatigue syndrome. *In Vivo.* 2005 Nov-Dec;19(6):1013-21. PMID: 16277015

The 2-5A synthetase/RNase L pathway in CFS patients appears to be both up-regulated (i.e. increased levels of bioactive 2-5A synthetase and increased activity of the RNase L enzyme) and deregulated (elastase and calpain initiate 83 kDa RNase L proteolysis, generating two major fragments with molecular masses of 37 and 30 kDa, respectively). The deregulation of the 2-5A synthetase/RNase L pathway in CFS accompanies decreased NK-function and deregulation of apoptotic pathways. Various components of the pathway appear to be related to performance during a graded exercise stress test.

*

Frémont M, El Bakkouri K, Vaeyens F, Herst CV, De Meirleir K, Englebienne P. 2',5'- Oligoadenylate size is critical to protect RNase L against proteolytic cleavage in chronic fatigue syndrome. *Exp Mol Pathol.* 2005 Jun;78(3):239-46. PMID: 15924878

CFS patients have disruptions in immune activity in the form of a dysregulation in the 2',5'-oligoadenylate (2-5A)-dependent RNase L antiviral pathway in peripheral blood mononuclear cells (PBMC) of CFS. This is characterized by upregulated 2-5A synthetase and RNase L activities, as well as by the presence of a low molecular weight (LMW) 2- 5A-binding protein of 37-kDa related to RNase L.

*

Tiev KP, Demettré E, Ercolano P, Bastide L, Lebleu B, Cabane J. RNase L levels in peripheral blood mononuclear cells: 37-kilodalton/83-kilodalton isoform ratio is a potential test for chronic fatigue syndrome. *Clin Diagn Lab Immunol.* 2003 Mar;10(2):315-6. PMID: 12626460

In the absence of acute infection or chronic inflammation, a high RNase L ratio could distinguish CFS patients from healthy volunteers.

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Demette E, Bastide L, D'Haese A, De Smet K, De Meirleir K, Tiev KP, Englebienne P, Lebleu B. Ribonuclease L proteolysis in peripheral blood mononuclear cells of chronic fatigue syndrome patients. *J Biol Chem.* 2002 Sep 20;277(38):35746-51. PMID: 12118002

A 37-kDa binding polypeptide accumulates in peripheral blood mononuclear cell (PBMC) extracts from CFS patients and is being considered as a potential diagnostic marker. The authors establish here that this low molecular weight 2-5A-binding polypeptide is a truncated form of the native 2-5A-dependent ribonuclease L (RNase L), generated by an increased proteolytic activity in CFS PBMC extracts.

*

Snell CR, Vanness JM, Strayer DR, Stevens SR. Physical performance and prediction of 2-5A synthetase/RNase L antiviral pathway activity in patients with chronic fatigue syndrome. *In Vivo.* 2002 Mar-Apr;16(2):107-9. PMID:12073768

Amongst a group of CFS patients, a group with elevated RNase L had a lower peak V_{O2} and duration than the normal group, but a higher performance score. The results suggest that both exercise testing and the RNase L biomarker have potential to aid in the diagnosis of CFS.

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Shetzline SE, Martinand-Mari C, Reichenbach NL, Buletic Z, Lebleu B, Pfliederer W, Charubala R, De Meirleir K, De Becker P, Peterson DL, Herst CV, Englebienne P, Suhadolnik RJ. Structural and functional features of the 37-kDa 2-5A-dependent RNase L in chronic fatigue syndrome. *J Interferon Cytokine Res.* 2002 Apr;22(4):443-56. PMID: 12034027

A 2',5'-oligoadenylate (2-5A)-dependent 37-kDa form of RNase L has been reported in extracts of peripheral blood mononuclear cells (PBMC) from individuals with chronic fatigue syndrome (CFS). The authors examined the biochemical relationship between the 80-kDa RNase L in healthy control PBMC and the 37-kDa RNase L in PBMC from individuals with CFS.

*

Vojdani A, Choppa PC, Lapp CW. Downregulation of RNase L inhibitor correlates with upregulation of interferon-induced proteins (2-5A synthetase and RNase L) in patients with chronic fatigue immune dysfunction syndrome. *J Clin Lab Immunol.* 1998;50(1):1- 16. PMID: 10189612

We investigated the levels of 2-5A synthetase, RNase L and RLI in patients with CFIDS and found a statistically significant decrease in RLI mRNA. The increased activation of RNase L may result in an increased cellular RNA turnover and subsequent inhibition of protein synthesis; thus resulting in general fatigue, myalgia muscle weakness and other symptomatology shown in CFIDS patients.

*

Suhadolnik RJ, Peterson DL, O'Brien K, Cheney PR, Herst CV, Reichenbach NL, Kon N, Horvath SE, Iacono KT, Adelson ME, De Meirleir K, De Becker P, Charubala R, Pfliederer W. Biochemical evidence for a novel low molecular weight 2-5A-dependent RNase L in chronic fatigue syndrome. *J Interferon Cytokine Res.* 1997 Jul;17(7):377-85. PMID: 9243369

The authors present evidence suggesting that the RNase L enzyme dysfunction in CFS is more complex than previously reported.

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Suhadolnik RJ, Reichenbach NL, Hitzges PM, Ablashi DV, Strayer DR, Carter WA. RNA drug therapy acting via the 2-5A synthetase/RNase L pathway. *Ann N Y Acad Sci.* 1993 Jun 23;685:756-7. PMID: 8363281

Mitochondria

Morris G, Maes M. Mitochondrial dysfunctions in myalgic encephalomyelitis/chronic fatigue syndrome explained by activated immuno-inflammatory, oxidative and nitrosative stress pathways. *Metab Brain Dis.* 2014 Mar;29(1):19-36. PMID: 24557875

ME/CFS is a neuro-immune disorder accompanied by chronic low-grade inflammation, increased levels of oxidative and nitrosative stress (O&NS), O&NS-mediated damage to fatty acids, DNA and proteins, autoimmune reactions directed against neoantigens and brain disorders. Mitochondrial dysfunctions have been found in ME/CFS, e.g. lowered ATP production, impaired oxidative phosphorylation and mitochondrial damage. This paper reviews the pathways that may explain mitochondrial dysfunctions in ME/CFS.

Morris G, Maes M. Myalgic encephalomyelitis/chronic fatigue syndrome and encephalomyelitis disseminata/multiple sclerosis show remarkable levels of similarity in phenomenology and neuroimmune characteristics. *BMC Med.* 2013 Sep 17;11:205. PMID: 24229326

Mitochondrial dysfunctions, including lowered levels of ATP, decreased phosphocreatine synthesis and impaired oxidative phosphorylation, are heavily involved in the pathophysiology of both MS and ME/CFS. The findings produced by neuroimaging techniques are quite similar in both illnesses and show decreased cerebral blood flow, atrophy, gray matter reduction, white matter hyperintensities, increased cerebral lactate and choline signaling and lowered acetyl-aspartate levels.

*

Meeus M, Nijs J, Hermans L, Goubert D, Calders P. The role of mitochondrial dysfunctions due to oxidative and nitrosative stress in the chronic pain or chronic fatigue syndromes and fibromyalgia patients: peripheral and central mechanisms as therapeutic targets? *Expert Opin Ther Targets.* 2013 Sep;17(9):1081-9. PMID: 23834645

The current evidence regarding oxidative and nitrosative stress and mitochondrial dysfunction in CFS and FM is presented in relation to chronic widespread pain.

*

Castro-Marrero J, Cordero MD, Sáez-Francas N, Jimenez-Gutierrez C, Aguilar-Montilla FJ, Aliste L, Alegre-Martin J. Could mitochondrial dysfunction be a differentiating marker between chronic fatigue syndrome and fibromyalgia? *Antioxid Redox Signal.* 2013 Nov 20;19(15):1855-60. PMID: 23600892

The researchers looked at the possible association between mitochondrial biogenesis and oxidative stress in patients with CFS vs. patients with fibromyalgia (FM) and healthy controls. Compared to controls, both CFS and FM patients had decreased levels of Coenzyme Q10, decreased ATP levels, and increased levels of

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lipid peroxidation.

Several measures (mitochondrial citrate synthase activity, mitochondrial DNA content and expression levels of peroxisome proliferator-activated receptor gamma-coactivator 1-alpha and transcription factor A, mitochondrial by immunoblotting) were significantly lower in FM patients than either CFS patients or controls.

*

Booth NE, Myhill S, McLaren-Howard J. Mitochondrial dysfunction and the pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). *Int J Clin Exp Med.* 2012;5(3):208-20. PMID: 22837795

Researchers found that all CFS patients tested had measurable mitochondrial dysfunction, correlating with the severity of the illness. The patients divide into two main groups differentiated by how cellular metabolism attempts to compensate for the dysfunction. The major immediate causes of the dysfunction are lack of essential substrates and partial blocking of the translocator protein sites in mitochondria.

*

Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E. Coenzyme Q10 deficiency in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is related to fatigue, autonomic and neurocognitive symptoms and is another risk factor explaining the early mortality in ME/CFS due to cardiovascular disorder. *Neuro Endocrinol Lett.* 2009;30(4):470-6. PMID: 20010505

CFS patients have very low levels of CoQ10, a mitochondrial nutrient that acts as a cofactor for ATP production and has antioxidant effects. This may be related to increased mortality from chronic heart failure in the disease.

*

Pietrangelo T, Mancinelli R, Toniolo L, Montanari G, Vecchiet J, Fanò G, Fulle S. Transcription profile analysis of vastus lateralis muscle from patients with chronic fatigue syndrome. *Int J Immunopathol Pharmacol.* 2009 Jul-Sep;22(3):795-807. PMID: 19822097

The expression of a number of genes in CFS are altered, including ones related to mitochondrial function and oxidative balance, energy production, muscular trophism, and neuromuscular transmission.

*

Hokama Y, Campora CE, Hara C, Kuribayashi T, Le Huynh D, Yabusaki K. Anticardiolipin antibodies in the sera of patients with diagnosed chronic fatigue syndrome. *J Clin Lab Anal.* 2009;23(4):210-2. PMID: 19623655

Anticardiolipin antibodies (an anti-mitochondrial antibody found in specific other diseases) were detected in an extremely high percentage of CFS patients.

*

Myhill S, Booth NE, McLaren-Howard J. Chronic fatigue syndrome and mitochondrial dysfunction. *Int J Clin Exp Med.* 2009;2(1):1-16. PMID: 19436827

Mitochondrial dysfunction is strongly associated with CFS.

Mathew SJ, Mao X, Keegan KA, Levine SM, Smith EL, Heier LA, Otcheretko V, Coplan JD, Shungu DC.

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Ventricular cerebrospinal fluid lactate is increased in chronic fatigue syndrome compared with generalized anxiety disorder: an in vivo 3.0 T (1)H MRS imaging study. *NMR Biomed.* 2009 Apr;22(3):251-8. PMID: 18942064

Compared to healthy controls and sufferers of anxiety disorder, CFS patients have significantly raised concentrations of ventricular lactate in their spinal fluid. This is potentially related to decreased cortical blood flow, secondary mitochondrial dysfunction and oxidative stress abnormalities.

*

Hokama Y, Empey-Campora C, Hara C, Higa N, Siu N, Lau R, Kuribayashi T, Yabusaki K. Acute phase phospholipids related to the cardiolipin of mitochondria in the sera of patients with chronic fatigue syndrome (CFS), chronic Ciguatera fish poisoning (CCFP), and other diseases attributed to chemicals, Gulf War, and marine toxins. *J Clin Lab Anal.* 2008;22(2):99-105. PMID: 18348309

Patients with CFS, chronic Ciguatera fish poisoning and Gulf War Illness were all more likely to demonstrate anticardiolipin antibody, associated with mitochondrial dysfunction.

Natural Killer Cells

Brenu EW, van Driel ML, Staines DR, Ashton KJ, Hardcastle SL, Keane J, Tajouri L, Peterson D, Ramos SB, Marshall-Gradisnik SM. Longitudinal investigation of natural killer cells and cytokines in chronic fatigue syndrome/myalgic encephalomyelitis. *J Transl Med.* 2012 May 9;10:88. PMID: 22571715

This study's results confirm decreases in immune function in CFS/ME patients, suggesting an increased susceptibility to viral and other infections. Furthermore, NK cytotoxic activity may be a suitable biomarker for diagnosing CFS/ME as it was consistently decreased during the course of the 12 months study.

*

Fletcher MA, Zeng XR, Maher K, Levis S, Hurwitz B, Antoni M, Broderick G, Klimas NG. Biomarkers in chronic fatigue syndrome: evaluation of natural killer cell function and dipeptidyl peptidase IV/CD26. *PLoS One.* 2010 May 25;5(5):e10817. PMID: 20520837

CFS patients display abnormal natural killer cell function, and this has potential as a biomarker for CFS.

*

Siegel SD, Antoni MH, Fletcher MA, Maher K, Segota MC, Klimas N. Impaired natural immunity, cognitive dysfunction, and physical symptoms in patients with chronic fatigue syndrome: preliminary evidence for a subgroup? *J Psychosom Res.* 2006 Jun;60(6):559-66. PMID: 16731230

Relative to CFS patients with normal Natural Killer Cell Activity (NKCA), low-NKCA patients reported less vigor, more daytime dysfunction, and more cognitive impairment. In addition, low-NKCA patients

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performed less on objective measures of cognitive functioning relative to normal-NKCA patients.

*

Robertson MJ, Schacterle RS, Mackin GA, Wilson SN, Bloomingdale KL, Ritz J, Komaroff AL. Lymphocyte subset differences in patients with chronic fatigue syndrome, multiple sclerosis and major depression. *Clin Exp Immunol.* 2005 Aug;141(2):326-32. PMID: 15996197

Compared to patients with multiple sclerosis, patients with CFS had greater numbers of CD16(+)/CD3(-) NK cells.

*

Ogawa M, Nishiura T, Yoshimura M, Horikawa Y, Yoshida H, Okajima Y, Matsumura I, Ishikawa J, Nakao H, Tomiyama Y, Kanayama Y, Kanakura Y, Matsuzawa Y. Decreased nitric oxide-mediated natural killer cell activation in chronic fatigue syndrome. *Eur J Clin Invest.* 1998 Nov;28(11):937-43. PMID: 9824439

In healthy control subjects, NK activity was significantly increased after treatment with L- Arg, an NK function enhancer, for 24 h, whereas the same treatment failed to enhance NK activity in the CFS patients. Further study results demonstrate that the L-Arg-induced activation of NK activity is mediated by NO and that a possible dysfunction exists in the NO-mediated NK cell activation in CFS patients.

*

Whiteside TL, Friberg D. Natural killer cells and natural killer cell activity in chronic fatigue syndrome. *Am J Med.* 1998 Sep 28;105(3A):27S-34S. PMID: 9790479

Low levels of natural killer cell activity have been reported in a significant percentage of cases in CFS.

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Levine PH, Whiteside TL, Friberg D, Bryant J, Colclough G, Herberman RB. Dysfunction of natural killer activity in a family with chronic fatigue syndrome. *Clin Immunol Immunopathol.* 1998 Jul;88(1):96-104. PMID: 9683556

Low NK activity some families may be a result of a genetically determined immunologic abnormality predisposing to CFS and cancer.

*

Ojo-Amaize EA, Conley EJ, Peter JB. Decreased natural killer cell activity is associated with severity of chronic fatigue immune dysfunction syndrome. *Clin Infect Dis.* 1994 Jan;18 Suppl 1:S157-9. PMID: 8148445

This data suggest a correlation between low levels of natural killer cell activity and severity of CFS.

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Aoki T, Miyakoshi H, Usuda Y, Herberman RB. Low NK syndrome and its relationship to chronic fatigue syndrome. *Clin Immunol Immunopathol.* 1993 Dec;69(3):253-65. PMID: 8242898

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Low natural killer cell function is associated with CFS.

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Uchida A. Chronic fatigue immune dysfunction syndrome. *Nihon Rinsho*. 1992 Nov;50(11):2625-9. PMID: 1287238

Restoration of NK activity was correlated with recovery from CFS in patients.

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Morrison LJ, Behan WH, Behan PO. Changes in natural killer cell phenotype in patients with post-viral fatigue syndrome. *Clin Exp Immunol*. 1991 Mar;83(3):441-6. PMID: 1706238

Authors found increased percentages of CD56+, and especially CD56bright+ NK cells in post-viral fatigue patients. They also found significantly increased percentages of CD56+ high affinity interleukin-2 (IL-2) receptor (CD25)+ and CD56+ transferrin receptor (CD71+) subsets of cells, most of which also stained brightly for CD56. They also found an increased percentage of CD56+ CD3+ cells, many of which stained brightly for CD56, although there was no increase in the percentage of CD56- CD3+ T cells in these patients. There also was a very low percentage of CD56- CD25+ cells and a decreased percentage of CD56+ Fc gamma receptor (CD16)+ NK cells.

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Caligiuri M, Murray C, Buchwald D, Levine H, Cheney P, Peterson D, Komaroff AL, Ritz J. Phenotypic and functional deficiency of natural killer cells in patients with chronic fatigue syndrome. *J Immunol*. 1987 Nov 15;139(10):3306-13. PMID: 2824604

A majority of patients with CFS have low numbers of NKH1+T3- lymphocytes, a population that represents the great majority of NK cells in normal individuals. Patients with CFS consistently demonstrated low levels of killing. After activation of cytolytic activity with recombinant interleukin 2, patients were able to display increased killing against K562 but most patients remained unable to lyse Epstein-Barr virus-infected B cell targets. Additional cytotoxicity experiments were carried out utilizing anti-T3 monoclonal antibody to block killing by NKH1+T3+ cells. These experiments indicated that the NK cell that appears to be responsible for much of the functional activity remaining in patients with CFS belongs to the NKH1+T3+ subset, which under normal circumstances represents only approximately 20% of the NK cell population.

Immune Abnormalities

Brenu EW, Huth TK, Hardcastle SL, Fuller K, Kaur M, Johnston S, Ramos SB, Staines DR, Marshall-Gradisnik SM. Role of adaptive and innate immune cells in chronic fatigue syndrome/myalgic encephalomyelitis. *Int Immunol*. 2014 Apr;26(4):233-42. PMID: 24343819

Thirty patients with CFS/ME and 25 non-fatigued controls were recruited for this study. Significant changes were observed in B-cell subsets, Tregs, CD4(+)CD73(+)CD39(+) T cells, cytotoxic activity, granzyme B, neutrophil antigens, TNF- α and IFN- γ in the CFS/ME patients in comparison with the non-fatigued controls. Alterations in B cells, Tregs, NK cells and neutrophils suggest significant impairments in immune regulation in CFS/ME.

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Curriu M, Carrillo J, Massanella M, Rigau J, Alegre J, Puig J, Garcia-Quintana AM, Castro-Marrero J, Negro E, Clotet B, Cabrera C, Blanco J. Screening NK-, B- and T- cell phenotype and function in patients suffering from Chronic Fatigue Syndrome. *J Transl Med.* 2013 Mar 20;11:68. PMID:23514202

CFS patients showed increased levels of T regulatory cells (CD25+/FOXP3+) CD4 T cells, and lower proliferative responses. Moreover, CD8 T cells from the CFS group showed significantly lower activation and frequency of effector memory cells. NK cells from CFS individuals displayed higher expression of NKp46 and CD69 but lower expression of CD25 in all NK subsets defined.

*

Bradley AS, Ford B, Bansal AS. Altered functional B cell subset populations in patients with chronic fatigue syndrome compared to healthy controls. *Clin Exp Immunol.* 2013 Apr;172(1):73-80. PMID: 23480187

Compared to healthy controls, CFS patients had greater numbers of naive B cells as a percentage of lymphocytes, greater numbers of naive B cells as a percentage of B cells, greater numbers of transitional B cells and reduced numbers of plasmablasts. The authors speculate whether this may suggest a subtle tendency to autoimmunity.

*

Brenu EW, Ashton KJ, van Driel M, Staines DR, Peterson D, Atkinson GM, Marshall- Gradisnik SM. Cytotoxic lymphocyte microRNAs as prospective biomarkers for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. *J Affect Disord.* 2012 Dec 10;141(2- 3):261-9. PMID: 22572093

There was a significant reduction in the expression levels of microRNA(miR)-21, in both the natural killer and CD8(+)T cells in the CFS/ME sufferers. Additionally, the expression of miR-17-5p, miR-10a, miR-103, miR-152, miR-146a, miR-106, miR-223 and miR-191 was significantly decreased in NK cells of CFS/ME patients in comparison to the non- fatigued controls.

*

Bansal AS, Bradley AS, Bishop KN, Kiani-Alikhan S, Ford B. Chronic fatigue syndrome, the immune system and viral infection. *Brain Behav Immun.* 2011 Jul 2. PMID: 21756995

CFS is a heterogeneous disorder with a common set of symptoms. Slightly increased parameters of inflammation and pro-inflammatory cytokines such as interleukin (IL) 1, IL6 and tumour necrosis factor (TNF) α are likely present. Additionally, impaired natural killer cell function appears evident. Alterations in T cell numbers have been described by some and not others. There is some evidence of viral persistence and inadequate containment of viral replication. The ability of certain herpes viruses to impair the development of T cell memory may explain this viral persistence and the continuation of symptoms.

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Brenu EW, Staines DR, Baskurt OK, Ashton KJ, Ramos SB, Christy RM, Marshall- Gradisnik SM. Immune and hemorheological changes in chronic fatigue syndrome. *J Transl Med.* 2010 Jan 11;8:1. PMID: 20064266

CFS patients (n = 10) had significant decreases in neutrophil respiratory burst, NK cytotoxic activity and CD56(bright)CD16(-) NK phenotypes in comparison to healthy controls (n = 10). Hemorheological characteristic, aggregation, deformability, fibrinogen,

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lymphocyte numbers and CD56(dim)CD16(+) NK cells were similar between the two groups.

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Meeus M, Mistiaen W, Lambrecht L, Nijs J. Immunological similarities between cancer and chronic fatigue syndrome: the common link to fatigue? *Anticancer Res.* 2009 Nov;29(11):4717-26. PMID: 20032425

CFS patients display a number of immunological abnormalities also seen in cancer, including abnormalities of ribonuclease (RNase) L, hyperactivation of nuclear factor kappa beta (NF-kappa B), high oxidative stress and natural killer cell malfunction.

*

Lorusso L, Mikhaylova SV, Capelli E, Ferrari D, Ngonga GK, Ricevuti G. Immunological aspects of chronic fatigue syndrome. *Autoimmun Rev.* 2009 Feb;8(4):287-91. PMID: 18801465

Immunological problems in CFS include an alteration in cytokine profile, a decreased function of natural killer (NK) cells, a presence of autoantibodies, and a reduced responses of T cells to mitogens and other specific antigens have been reported. The observed high level of pro-inflammatory cytokines may explain some of the manifestations such as fatigue and flu-like symptoms and influence NK activity. Abnormal activation of the T lymphocyte subsets and a decrease in antibody-dependent cell-mediated cytotoxicity have been described. An increased number of CD8+ cytotoxic T lymphocytes and CD38 and HLA-DR activation markers have been reported, and a decrease in CD11b expression associated with an increased expression of CD28+ T subsets has been observed.

*

Torres-Harding S, Sorenson M, Jason LA, Maher K, Fletcher MA. Evidence for T-helper 2 shift and association with illness parameters in chronic fatigue syndrome (CFS). *Bull IACFS ME.* 2008 Fall;16(3):19-33. PMID: 21234277

This investigation measured the percentage of Th1-like and Th2-like memory cells using cell surface flow cytometry in 114 individuals with CFS. Results indicated that individuals who exhibited a more extreme shift towards a Th2 immune response also exhibited poorer sleep and high levels of basal salivary cortisol. The implications of these findings are discussed.

*

Meeus M, Nijs J, McGregor N, Meeusen R, De Schutter G, Truijen S, Frémont M, Van Hoof E, De Meirleir K. Unravelling intracellular immune dysfunctions in chronic fatigue

syndrome: interactions between protein kinase R activity, RNase L cleavage and elastase activity, and their clinical relevance. *In Vivo.* 2008 Jan-Feb;22(1):115-21. PMID: 18396793

CFS patients have a variety of immunological abnormalities, including Rnase L-cleavage, protein kinase R and elastase activity.

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Aspler AL, Bolshin C, Vernon SD, Broderick G. Evidence of inflammatory immune signaling in chronic fatigue syndrome: A pilot study of gene expression in peripheral blood. *Behav Brain Funct.* 2008 Sep 26;4:44. PMID: 18822143

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CFS patients have B cell dysfunction with coordinated immune activation supporting persistent inflammation and antibody-mediated NK cell modulation of T cell activity. The CD19+ genes have potential as a biomarker.

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Mihaylova I, DeRuyter M, Rummens JL, Bosmans E, Maes M. Decreased expression of CD69 in chronic fatigue syndrome in relation to inflammatory markers: evidence for a severe disorder in the early activation of T lymphocytes and natural killer cells. *Neuro Endocrinol Lett.* 2007 Aug;28(4):477-83. PMID: 17693977

The expression of the CD69 activation marker on T cells (CD3+, CD3+CD4+, and CD3+CD8+) and on NK cells (CD45+CD56+) was significantly lower in CFS patients than in healthy subjects, indicating immune abnormalities.

*

Maher KJ, Klimas NG, Fletcher MA. Chronic fatigue syndrome is associated with diminished intracellular perforin. *Clin Exp Immunol.* 2005 Dec;142(3):505-11. PMID: 16297163

CFS patients had a significant reduction in the NK cell associated perforin levels and a reduced perforin level within the cytotoxic T cells.

*

Kennedy G, Spence V, Underwood C, Belch JJ. Increased neutrophil apoptosis in chronic fatigue syndrome. *J Clin Pathol.* 2004 Aug;57(8):891-3. PMID: 15280416

CFS patients had higher numbers of apoptotic neutrophils, lower numbers of viable neutrophils, increased annexin V binding, and increased expression of the death receptor, tumour necrosis factor receptor-I, on their neutrophils than did the 34 healthy controls. Patients with CFS also had raised concentrations of active TGFbeta1.

Sabath DE, Barcy S, Koelle DM, Zeh J, Ashton S, Buchwald D. Cellular immunity in monozygotic twins discordant for chronic fatigue syndrome. *J Infect Dis.* 2002 Mar 15;185(6):828-32. PMID: 11920301

The objective of this study was to assess the nature and extent of abnormalities in lymphocyte cell surface markers and NK cell activity in patients with CFS while controlling for genetic factors. In a twin study, significantly greater variability was noted in twins discordant for CFS than in the concordant healthy twins for 20 of 48 variables examined.

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Patarca R. Cytokines and chronic fatigue syndrome. *Ann N Y Acad Sci.* 2001 Mar;933:185-200. PMID:12000020

Chronic fatigue syndrome (CFS) patients show evidence of immune activation, as demonstrated by increased numbers of activated T lymphocytes, including cytotoxic T cells, as well as elevated levels of circulating cytokines. Nevertheless, immune cell function of CFS patients is poor, with low natural killer cell cytotoxicity (NKCC), poor lymphocyte response to mitogens in culture, and frequent immunoglobulin deficiencies, most often IgG1 and IgG3. Immune dysfunction in CFS, with predominance of so-called T-helper type 2 and proinflammatory cytokines, can be episodic and associated with either cause or effect of the physiological and psychological function derangement and/or activation of latent viruses or other pathogens.

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Visser J, Blauw B, Hinloopen B, Brommer E, de Kloet ER, Kluft C, Nagelkerken L. CD4 T lymphocytes from patients with chronic fatigue syndrome have decreased interferon- gamma production and increased sensitivity to dexamethasone. *J Infect Dis.* 1998 Feb;177(2):451-4. PMID: 9466535

CD4 T cells from CFS patients produced less interferon-gamma than did cells from controls. With CD4 T cells from CFS patients (compared with cells from controls), a 10- to 20-fold lower DEX concentration was needed to achieve 50% inhibition of interleukin- 4 production and proliferation, indicating an increased sensitivity to DEX in CFS patients. A differential sensitivity of cytokines or CD4 T cell subsets to glucocorticoids might explain an altered immunologic function in CFS patients.

*

Vojdani A, Ghoneum M, Choppa PC, Magtoto L, Lapp CW. Elevated apoptotic cell population in patients with chronic fatigue syndrome: the pivotal role of protein kinase RNA. *J Intern Med.* 1997 Dec;242(6):465-78. PMID: 9437407

Increased apoptotic cell population in peripheral blood lymphocytes was observed in CFS individuals. This was accompanied by an abnormal cell arrest in the S phase and the G2/M boundary of the cell cycle and by enhanced PKR mRNA and protein levels as compared to healthy controls. Protein kinase RNA-mediated apoptosis in CFS individuals may contribute to the pathogenesis and the fatigue symptomatology associated with CFS.

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Mawle AC, Nisenbaum R, Dobbins JG, Gary HE Jr, Stewart JA, Reyes M, Steele L, Schmid DS, Reeves WC. Immune responses associated with chronic fatigue syndrome: a case-control study. *J Infect Dis.* 1997 Jan;175(1):136-41. PMID: 8985207

Immune responses of CFS patients compared to normal people were more pronounced when they were grouped by type of disease onset (gradual or sudden) or by how they were feeling on the day of the test.

*

Tirelli U, Marotta G, Improta S, Pinto A. Immunological abnormalities in patients with chronic fatigue syndrome. *Scand J Immunol.* 1994 Dec;40(6):601-8. PMID: 7997849

The authors examined blood of CFS patients. Whilst no significant differences were found in the absolute numbers of circulating total T cells (CD3+) and of total helper/inducer (CD4+) or suppressor/cytotoxic (CD8+) T cells, an evident reduction in CD3-/CD16+ and CD57+/CD56+ NK lymphocytes along with an expansion of the CD8+/CD56+ and CD16-/CD56+ NK subsets, were found in the CFS group. In addition, CD56+ NK cells from CFS subjects were found to express an increased amount of cell adhesion molecules (CD11b, CD11c, CD54) and activation antigens (CD38). Both the percentage and absolute numbers of CD4+ T cells bearing the CD45RA antigen appeared significantly reduced in CFS patients, and CD4+ T lymphocytes from CFS subjects displayed an increased expression of the intercellular adhesion molecule-1 (ICAM-1/CD54). Finally, the total numbers of circulating (CD19+) B lymphocytes, were significantly higher in CFS cases than in controls, and in 11 out of 30 CFS patients the increase in circulating B cells was sustained by the expansion of the CD5+/CD19+ subset of B lymphocytes.

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Levy JA. Viral studies of chronic fatigue syndrome. *Clin Infect Dis.* 1994 Jan;18 Suppl 1:S117-20. PMID: 8148437

Immunologic studies have demonstrated activated CD8+ cells and reduced function of natural killer cells suggesting a host response to an infection that has led to persistent immune disorders. Some of the symptoms of CFS may be due to cytokines produced by this hyperactive immune response to a virus that is still present in the host or that has been eliminated but leaves abnormal immunologic sequelae.

Barker E, Fujimura SF, Fadem MB, Landay AL, Levy JA. Immunologic abnormalities associated with chronic fatigue syndrome. *Clin Infect Dis.* 1994 Jan;18 Suppl 1:S136-41. PMID: 8148441

Compared with those of healthy individuals, CFS patients' CD8+ T cells expressed reduced levels of CD11b and expressed the activation markers CD38 and HLA-DR at elevated levels. In many of the individuals in whom expression of CD11b was reduced the expression of CD28 was increased. These findings indicate expansion of a population of activated CD8+ cytotoxic T lymphocytes. A marked decrease in NK cell activity was found in almost all patients with CFS.

*

Straus SE, Fritz S, Dale JK, Gould B, Strober W. Lymphocyte phenotype and function in the chronic fatigue syndrome. *J Clin Immunol.* 1993 Jan;13(1):30-40. PMID: 8095270

Compared to controls, in CFS patients the percentage of CD4 T cells and CD4,CD45RA, or naive T cells, was reduced. The CD4,CD45RO, or memory T-cell, subset was numerically normal but expressed increased levels of adhesion markers (CD29, CD54, and CD58). CFS patient lymphocytes showed reduced proliferative responses to phytohemagglutinin, concanavalin A, and staphylococcal enterotoxin B.

*

Lloyd A, Hickie I, Hickie C, Dwyer J, Wakefield D. Cell-mediated immunity in patients with chronic fatigue syndrome, healthy control subjects and patients with major depression. *Clin Exp Immunol.* 1992 Jan;87(1):76-9. PMID: 1733640

Patients with CFS demonstrated impaired lymphocyte responses to phytohaemagglutinin (PHA) stimulation, and reduced or absent delayed-type hypersensitivity (DTH) skin responses.

*

Landay AL, Jessop C, Lennette ET, Levy JA. Chronic fatigue syndrome: clinical condition associated with immune activation. *Lancet.* 1991 Sep 21;338(8769):707-12. PMID: 1679864

CAreduced CD8 suppressor cell population and increased activation markers (CD38, HLA-DR) on CD8 cells were found in CFS sufferers.

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Gupta S, Vayuvegula B. A comprehensive immunological analysis in chronic fatigue syndrome. *Scand J Immunol.* 1991 Mar;33(3):319-27. PMID: 1849315

Natural killer cells as defined by CD16, CD56 and CD57 antigens were significantly reduced in a group of CFS patients. A significant increase in the proportions of CD4+ ICAM 1+ T cells was observed in CFS. Monocytes from CFS displayed increased density (as determined by mean fluorescence channel numbers) of intercellular adhesion molecule 1 (ICAM-1) and lymphocyte function associated antigen 1

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(LFA-1), but showed decreased enhancing response to recombinant interferon-gamma in vitro. The lymphocyte DNA synthesis in response to phytohaemagglutinin (PHA), Concanavalin A (Con A) and pokeweed mitogen (PWM) was normal but the response to soluble antigens was significantly reduced. In vivo specific antibody response to pneumococcus vaccine was depressed in CFS. Forty percent of patients showed titres of anti-human herpes virus 6 (anti-HHV-6) antibody higher than that in the controls (greater than or equal to 1/80).

*

Klimas NG, Salvato FR, Morgan R, Fletcher MA. Immunologic abnormalities in chronic fatigue syndrome. *J Clin Microbiol.* 1990 Jun;28(6):1403-10. PMID: 2166084

CFS patients immunological abnormalities are profiled. The most consistent was low natural killer (NK) cell cytotoxicity. The number of NK cells, as defined by reactivity with monoclonal antibody NKH.1 (CD56), was elevated, but the killing of K562 tumor cells per CD56 cell was significantly diminished. Lymphoproliferative responses after stimulation with phytohemagglutinin and pokeweed mitogen were decreased in most patients, as was the production of gamma interferon following mitogen stimulation. Lymphocyte phenotypic marker analysis of peripheral blood lymphocytes showed that there were significant differences between patients with CFS and controls. There was an increase in the percentage of suppressor-cytotoxic T lymphocytes, CD8, and a proportionally larger increase in the number of CD8 cells expressing the class II activation marker. Most patients had an elevated number of CD2 cells which expressed the activation marker CDw26. The numbers of CD4 cells and the helper subset of CD4+CD29+ cells in patients with CFS were not different from those in controls. There was, however, a significant decrease in the suppressor inducer subset of CD4+ CD45RA+ cells. The number of B cells, CD20 and CD21, were elevated, as were the numbers of a subset of B cells which coexpressed CD20 and CD5.

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Lloyd AR, Wakefield D, Boughton CR, Dwyer JM. Immunological abnormalities in the chronic fatigue syndrome. *Med J Aust.* 1989 Aug 7;151(3):122-4. PMID: 2787888

In patients with CFS, a significant reduction was found in the absolute number of peripheral blood lymphocytes in the total T-cell (CD2), the helper/inducer T-cell (CD4) and the suppressor/cytotoxic T-cell (CD8) subsets. A significant reduction also was found

in T-cell function. Reduced immunoglobulin (Ig) levels were common (56% of patients), with the levels of serum IgG3- and IgG1-subclasses particularly affected.

Autoimmune Issues

Maes M, Ringel K, Kubera M, Anderson G, Morris G, Galecki P, Geffard M. In myalgic encephalomyelitis/chronic fatigue syndrome, increased autoimmune activity against 5-HT is associated with immuno-inflammatory pathways and bacterial translocation. *J Affect Disord.* 2013 Sep 5;150(2):223-30. PMID: 23664637

The incidence of positive autoimmune activity against serotonin was significantly higher in ME/CFS than in patients with chronic fatigue or controls. ME/CFS patients with 5-HT autoimmune activity displayed higher TNF α , IL-1 and neopterin and increased IgA responses against LPS of commensal bacteria than those without 5-HT autoimmune activity. Anti-5-HT antibody positivity was significantly associated with increased

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scores on hyperalgesia, fatigue, neurocognitive and autonomic symptoms, sadness and a flu-like malaise.

Herpesviruses

Jason LA, Katz BZ, Shiraishi Y, Mears CJ, Im Y, Taylor R. Predictors of Post-Infectious Chronic Fatigue Syndrome in Adolescents. *Health Psychol Behav Med.* 2014 Jan 1;2(1):41-51. PMID: 24660116

This study focused on identifying risk factors for the acquisition of CFS in adolescents following Infectious Mononucleosis. A number of variables were predictors of post-infectious CFS at 6 months; however, when autonomic symptoms were used as a control variable, only days spent in bed since mono was a significant predictor.

*

Loebel M, Strohschein K, Giannini C, Koelsch U, Bauer S, Doebis C, Thomas S, Unterwalder N, von Baehr V, Reinke P, Knops M, Hanitsch LG, Meisel C, Volk HD, Scheibenbogen C. Deficient EBV-specific B- and T-cell response in patients with chronic fatigue syndrome. *PLoS One.* 2014 Jan 15;9(1):e85387. PMID: 24454857

The authors analyzed the EBV-specific memory B- and T-cell response in patients with CFS. While they observed no difference in viral capsid antigen (VCA)-IgG antibodies, EBV nuclear antigen (EBNA)-IgG titers were low or absent in 10% of CFS patients.

When analyzing the EBV-specific memory B-cell reservoir in vitro a diminished or absent number of EBNA-1- and VCA-antibody secreting cells was found in up to 76% of

patients. They proposed a deficient EBV-specific B- and T-cell memory response in CFS patients and suggest an impaired ability to control early steps of EBV reactivation.

*

Tsai SY, Yang TY, Chen HJ, Chen CS, Lin WM, Shen WC, Kuo CN, Kao CH. Increased risk of chronic fatigue syndrome following herpes zoster: a population-based study. *Eur J Clin Microbiol Infect Dis.* 2014 Apr 9. PMID: 24715153

Researchers in Taiwan identified more than 9,000 patients with herpes zoster (HZ) infection and 36,000 patients without herpes zoster infections. The incidence rate of CFS was higher in the HZ cohort than in the non-HZ cohort.

*

Oakes B, Hoagland-Henefield M, Komaroff AL, Erickson JL, Huber BT. Human endogenous retrovirus-k18 superantigen expression and human herpesvirus-6 and human herpesvirus-7 viral loads in chronic fatigue patients. *Clin Infect Dis.* 2013 May;56(10):1394-400. PMID:23408682

The authors fail to demonstrate a difference in HERV-K18 env transcripts, HHV-6 viral copy number, and HHV-7 viral copy number between CFS patients and healthy controls.

*

Burbelo PD, Bayat A, Wagner J, Nutman TB, Baraniuk JN, Iadarola MJ. No serological evidence for a role

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of HHV-6 infection in chronic fatigue syndrome. *Am J Transl Res.* 2012;4(4):443-51. PMID: 23145212

No statistically significant differences in antibody levels or frequency of HHV-6A or HHV-6B infection were detected between the controls and CFS patients.

*

Chapenko S, Krumina A, Logina I, Rasa S, Chistjakovs M, Sultanova A, Viksna L, Murovska M. Association of active human herpesvirus-6, -7 and parvovirus b19 infection with clinical outcomes in patients with myalgic encephalomyelitis/chronic fatigue syndrome. *Adv Virol.* 2012;2012:205085. PMID: 22927850

Active viral infection with HHV6, HHV7 and/or parvovirus B19 was found in 64.8% of patients and in 13.3% of practically healthy persons. Increase in peripheral blood leukocyte DNA HHV-6 load as well as in proinflammatory cytokines' levels was detected in patients during active viral infection.

*

Lerner AM, Ariza ME, Williams M, Jason L, Beqaj S, Fitzgerald JT, Lemeshow S, Glaser R. Antibody to Epstein-Barr virus deoxyuridine triphosphate nucleotidohydrolase and deoxyribonucleotide polymerase in a chronic fatigue syndrome subset. *PLoS One.* 2012;7(11):e47891. PMID: 23155374

There is prolonged elevated antibody level against the encoded proteins EBV dUTPase and EBV DNA polymerase in a subset of CFS patients.

*

Shapiro JS. Does varicella-zoster virus infection of the peripheral ganglia cause Chronic Fatigue Syndrome? *Med Hypotheses.* 2009 Nov;73(5):728-34. PMID: 19520522

This article posits that infection of the peripheral ganglia causes at least some cases of Chronic Fatigue Syndrome (CFS), with a neurotropic herpesvirus, particularly varicella-zoster virus (VZV), as the most likely cause of the infection.

*

Beqaj SH, Lerner AM, Fitzgerald JT. Immunoassay with cytomegalovirus early antigens from gene products p52 and CM2 (UL44 and UL57) detects active infection in patients with chronic fatigue syndrome. *J Clin Pathol.* 2008 May;61(5):623-6. PMID: 18037660

Immunoassays that use early antigen recombinant HCMV CM(2) and p52 are five times more sensitive than HCMV ELISA assay using viral lysate, and are specific in the detection and differentiation of active human cytomegalovirus infection in a subset of patients with CFS.

*

Bellmann-Weiler R, Schroecksadel K, Holzer C, Larcher C, Fuchs D, Weiss G. IFN-gamma mediated pathways in patients with fatigue and chronic active Epstein Barr virus-infection. *J Affect Disord.* 2008 May;108(1-2):171-6. PMID: 17945348

EBV viremia in CFS is associated with cell-mediated immune activation and increased tryptophan degradation.

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Kondo K. Chronic fatigue syndrome and herpesvirus reactivation. *Nihon Rinsho*. 2007 Jun;65(6):1043-8. PMID: 17561695

The amount of HHV-6 and HHV-7 reactivation has potential as a biomarker for CFS.

*

Komaroff AL, Jacobson S, Ablashi DV, Yamanishi K. Highlights from 5th International Conference on HHV-6 and -7. *Herpes*. 2006 Nov;13(3):81-2. PMID: 17147913

HHV-6 enhances the progression of simian immunodeficiency virus in monkeys.

*

Chapenko S, Krumina A, Kozireva S, Nora Z, Sultanova A, Viksna L, Murovska M. Activation of human herpesviruses 6 and 7 in patients with chronic fatigue syndrome. *J Clin Virol*. 2006 Dec;37 Suppl 1:S47-51. PMID: 17276369

Reactivation of HHV6 and HHV7 in combination is frequent in CFS patients.

*

Komaroff AL. Is human herpesvirus-6 a trigger for chronic fatigue syndrome? *J Clin Virol*. 2006 Dec;37 Suppl 1:S39-46. PMID: 17276367

HHV6 is common in CFS and may serve to trigger and perpetuate the disease.

*

Kondo K. Human herpesvirus latency and fatigue. *Uirusu*. 2005 Jun;55(1):9-17. PMID:16308525

HHV-6 established latency in the macrophage, kept a fairly stable intermediate stage between latency and reactivation, and the viral reactivation was induced by two or more factors. HHV-6 is reactivated during work-induced fatigue, and HHV-6 reactivation can be an objective biomarker for fatigue.

*

Lerner AM, Beqaj SH, Deeter RG, Fitzgerald JT. IgM serum antibodies to Epstein-Barr virus are uniquely present in a subset of patients with the chronic fatigue syndrome. *In Vivo*. 2004 Mar-Apr;18(2):101-6. PMID: 15113035

Serum antibody to EBV VCA IgM may be a specific diagnostic test for a subset of CFS patients.

*

Lerner AM, Beqaj SH, Deeter RG, Fitzgerald JT. IgM serum antibodies to human cytomegalovirus nonstructural gene products p52 and CM2(UL44 and UL57) are uniquely present in a subset of patients with chronic fatigue syndrome. *In Vivo*. 2002 May- Jun;16(3):153-9. PMID: 12182109

The study suggests a relationship between CFS and human cytomegalovirus.

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Koelle DM, Barcy S, Huang ML, Ashley RL, Corey L, Zeh J, Ashton S, Buchwald D. Markers of viral infection in monozygotic twins discordant for chronic fatigue syndrome. *Clin Infect Dis*. 2002 Sep 1;35(5):518-25. PMID: 12173124

Identical twins discordant for CFS did not show differences on PCR assays for viral DNA for HHV-6, HHV-7, HHV-8, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, varicella zoster virus, JC virus, BK virus, or parvovirus B19.

*

Krueger GR, Koch B, Hoffmann A, Rojo J, Brandt ME, Wang G, Buja LM. Dynamics of chronic active herpesvirus-6 infection in patients with chronic fatigue syndrome: data acquisition for computer modeling. *In Vivo*. 2001 Nov-Dec;15(6):461-5. PMID: 11887330

Persistent low-dose stimulation by HHV-6 may favor imbalanced immune response rather than overt immune deficiency.

*

Reeves WC, Stamey FR, Black JB, Mawle AC, Stewart JA, Pellett PE. Human herpesviruses 6 and 7 in chronic fatigue syndrome: a case-control study. *Clin Infect Dis*. 2000 Jul;31(1):48-52. PMID: 10913395

The authors found no evidence that active or latent infection with HHV-6A, HHV-6B, HHV-7, or any combination these 3 HHVs is associated with chronic fatigue syndrome. [PubMed - indexed for MEDLINE]

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Ablashi DV, Eastman HB, Owen CB, Roman MM, Friedman J, Zabriskie JB, Peterson DL, Pearson GR, Whitman JE. Frequent HHV-6 reactivation in multiple sclerosis (MS) and chronic fatigue syndrome (CFS) patients. *J Clin Virol*. 2000 May;16(3):179-91. PMID: 10738137

In both MS and CFS patients, the authors found increased levels of HHV-6 antibody and HHV-6 DNA. A decrease in cellular immune responses was also detected in CFS patients.

*

Wallace HL 2nd, Natelson B, Gause W, Hay J. Human herpesviruses in chronic fatigue syndrome. *Clin Diagn Lab Immunol*. 1999 Mar;6(2):216-23. PMID: 10066657

Serological analyses of serum anti-EBV and anti-HHV6 antibody titers showed no significant differences between the CFS and control patients. [PubMed - indexed for MEDLINE]

*

Cuende JI, Civeira P, Diez N, Prieto J. High prevalence without reactivation of herpes virus 6 in subjects with chronic fatigue syndrome. *An Med Interna*. 1997 Sep;14(9):441-4. PMID: 9453750

The study showed a high proportion of CFS patients infected with HHV-6 but with low viral load.

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Buchwald D, Ashley RL, Pearlman T, Kith P, Komaroff AL. Viral serologies in patients with chronic fatigue and chronic fatigue syndrome. *Med Virol*. 1996 Sep;50(1):25-30. PMID: 8890037

Differences in the seroprevalence or GMTs of antibodies to 13 viruses were not consistently found in those with chronic fatigue compared with control subjects, or in any subsets of patients including those with CFS, an acute onset of illness, or a documented fever.

*

Schmalting KB, Jones JF. MMPI profiles of patients with chronic fatigue syndrome. *J Psychosom Res*. 1996 Jan;40(1):67-74. PMID: 8730646

EBV titers were higher among CFS patients and were associated with being more symptomatic.

*

Patnaik M, Komaroff AL, Conley E, Ojo-Amaize EA, Peter JB. Prevalence of IgM antibodies to human herpesvirus 6 early antigen (p41/38) in patients with chronic fatigue syndrome. *J Infect Dis*. 1995 Nov;172(5):1364-7. PMID: 7594679

More CFS patients than controls had elevated levels of HHV-6 EA-specific IgM, perhaps indicating active replication of HHV-6 in CFS.

*

Swanink CM, van der Meer JW, Vercoulen JH, Bleijenberg G, Fennis JF, Galama JM. Epstein-Barr virus (EBV) and the chronic fatigue syndrome: normal virus load in blood

and normal immunologic reactivity in the EBV regression assay. *Clin Infect Dis*. 1995 May;20(5):1390-2. PMID: 7620030

The authors failed to demonstrate a role for reactivation of EBV in CFS.

*

Di Luca D, Zorzenon M, Mirandola P, Colle R, Botta GA, Cassai E. Human herpesvirus 6 and human herpesvirus 7 in chronic fatigue syndrome. *J Clin Microbiol*. 1995 Jun;33(6):1660-61. PMID: 7650209

HHV-7 was present in over 80% of CFS patients and healthy controls, while the prevalence of HHV-6 variant A increased significantly in CFS cases (22 versus 4%; $P = 0.05$).

*

Sairenji T, Yamanishi K, Tachibana Y, Bertoni G, Kurata T. Antibody responses to Epstein-Barr virus, human herpesvirus 6 and human herpesvirus 7 in patients with chronic fatigue syndrome. *Intervirol*. 1995;38(5):269-73. PMID: 8724857

The results suggest that CFS patients may have reactivations of EBV, HHV-6 and HHV- 7.

*

Manian FA. Simultaneous measurement of antibodies to Epstein-Barr virus, human herpesvirus 6, herpes simplex virus types 1 and 2, and 14 enteroviruses in chronic fatigue syndrome: is there evidence of

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activation of a nonspecific polyclonal immune response? Clin Infect Dis. 1994 Sep;19(3):448-53. PMID: 7811864

In the majority of cases of CFS, elevation of viral antibody titers does not seem to be due to a nonspecific polyclonal immune response.

*

Yalcin S, Kuratsune H, Yamaguchi K, Kitani T, Yamanishi K. Prevalence of human herpesvirus 6 variants A and B in patients with chronic fatigue syndrome. Microbiol Immunol. 1994;38(7):587-90. PMID: 7968694

The results suggest active replication of HHV-6 in patients with CFS.

*

Natelson BH, Ye N, Moul DE, Jenkins FJ, Oren DA, Tapp WN, Cheng YC. High titers of anti-Epstein-Barr virus DNA polymerase are found in patients with severe fatiguing illness. J Med Virol. 1994 Jan;42(1):42-6. PMID: 8308519

Antibodies against EBV DNAP may be a useful marker in delineating a subset of patients with severe fatiguing illness.

*

Wray BB, Gaughf C, Chandler FW Jr, Berry SS, Latham JE, Wood L, DuRant RH. Detection of Epstein-Barr virus and cytomegalovirus in patients with chronic fatigue. Ann Allergy. 1993 Sep;71(3):223-6. PMID: 8396863

Epstein-Barr virus-DNA was detected more frequently in male CFS patients, 5/9 (55.6%), than controls, 0/6 (0%), but there was no difference in frequency in female patients, 4/32 (12.5%), than control subjects, 1/29 (3.4%). Cytomegalovirus-DNA was detected infrequently in patients and controls, 13% versus 22% respectively. The presence of EBV-DNA did not correlate with antibody titers nor with the complaint of sore throat.

*

Bond PA. A role for herpes simplex virus in the aetiology of chronic fatigue syndrome and related disorders. Med Hypotheses. 1993 May;40(5):301-8. PMID: 8394501

*

Lusso P, Malnati MS, Garzino-Demo A, Crowley RW, Long EO, Gallo RC. Infection of natural killer cells by human herpesvirus 6. Nature. 1993 Apr 1;362(6419):458-62. PMID: 7681936

Herpesvirus can directly target and kill NK cells, a potential strategy to suppress the natural anti-viral immunity of the host.

*

Kawai K, Kawai A. Studies on the relationship between chronic fatigue syndrome and Epstein-Barr virus in Japan. Intern Med. 1992 Mar;31(3):313-8. PMID: 1319246

Results of the study suggest that a relationship exists between CFS and EBV.

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*

Woodward CG, Cox RA. Epstein-Barr virus serology in the chronic fatigue syndrome. *J Infect.* 1992 Mar;24(2):133-9. PMID: 1314860

CFS patients who displayed elevated titres of antibodies to Early Antigens of EBV did not differ clinically from those displaying titres in the control range. Four of nine patients who had increased antibodies to Early Antigens also had evidence of active enterovirus infection.

*

Nishikai M. Chronic fatigue syndrome--study of 51 cases treated at the Second Tokyo National Hospital. *Nihon Rinsho.* 1992 Nov;50(11):2641-7. PMID: 1337560

In a group of CFS patients, IgG antibody titers to EB virus viral capsid antigen were more elevated in the CFS patient group compared to that of the control, and the mean number of NK cells was lower.

*

Josephs SF, Henry B, Balachandran N, Strayer D, Peterson D, Komaroff AL, Ablashi DV. HHV-6 reactivation in chronic fatigue syndrome. *Lancet.* 1991 Jun 1;337(8753):1346-7. PMID: 1674318

HHV-6 is reported to be reactivated in CFS.

*

Bertram G, Dreiner N, Krueger GR, Ramon A, Ablashi DV, Salahuddin SZ, Balachandram N. Frequent double infection with Epstein-Barr virus and human herpesvirus-6 in patients with acute infectious mononucleosis. *In Vivo.* 1991 May-Jun;5(3):271-9. PMID: 1654150

CFS is associated with reactivated HHV-6 and Epstein Barr Virus.

*

Jones JF, Streib J, Baker S, Herberger M. Chronic fatigue syndrome: I. Epstein-Barr virus immune response and molecular epidemiology. *J Med Virol.* 1991 Mar;33(3):151-8. PMID: 1679118

The study analyzed spontaneous transformation rates of peripheral blood lymphocytes, EBV viral genome characteristics as determined by DNA restriction fragment polymorphisms, and antibody production by Western blot analysis. Thirty percent of CFS patients versus 8% of control subjects underwent spontaneous transformation in the two studies. Western blot studies suggested that ill subjects made antibodies to lytic proteins more frequently than did healthy control subjects.

*

Buchwald D, Freedman AS, Ablashi DV, Sullivan JL, Caligiuri M, Weinberg DS, Hall CG, Ashley RL, Saxinger C, Balachandran N, et al. A chronic "postinfectious" fatigue syndrome associated with benign lymphoproliferation, B-cell proliferation, and active replication of human herpesvirus-6. *J Clin Immunol.* 1990 Nov;10(6):335-44. PMID: 1964694

A patient with ME and HHV6 is profiled.

*

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Gold D, Bowden R, Sixbey J, Riggs R, Katon WJ, Ashley R, Obrigewitch RM, Corey L. Chronic fatigue. A prospective clinical and virologic study. JAMA. 1990 Jul 4;264(1):48- 53. PMID: 2162397

No evidence of ongoing EBV infection with either transforming or nontransforming strains was demonstrated in this population of CFS patients.

*

Jones JF, Williams M, Schooley RT, Robinson C, Glaser R. Antibodies to Epstein-Barr virus-specific DNase and DNA polymerase in the chronic fatigue syndrome. Arch Intern Med. 1988 Sep;148(9):1957-60. PMID: 2843138

Antibodies acting against EBV-specific DNase and DNA polymerase, which are expressed only during virus replication, were assayed. Three of the six patients with elevated anti-EBV enzyme antibody levels developed fatal lymphomas.

*

Ablashi DV, Josephs SF, Buchbinder A, Hellman K, Nakamura S, Llana T, Lusso P, Kaplan M, Dahlberg J, Memon S, et al. Human B-lymphotropic virus (human herpesvirus- 6). J Virol Methods. 1988 Sep;21(1-4):29-48. PMID: 2846617

Human B-lymphotropic virus (HBLV), also known as human herpesvirus-6 (HHV-6), is elevated in AIDS patients and patients with chronic fatigue syndrome.

Enteroviruses

Chia J, Chia A, Voeller M, Lee T, Chang R. Acute enterovirus infection followed by myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and viral persistence. J Clin Pathol. 2010 Feb;63(2):165-8. PMID: 19828908

Three representative patients with different manifestations of acute enterovirus infections progressed to have chronic symptoms of ME/CFS. Persistent viral infection was

demonstrated in the antrum years later. Chronic enterovirus infection in an immunocompetent host may be an example of a stalemate between attenuated, intracellular viruses and an ineffective immune response.

*

Chia JK, Chia AY. Chronic fatigue syndrome is associated with chronic enterovirus infection of the stomach. J Clin Pathol. 2008 Jan;61(1):43-8. PMID: 17872383

Enterovirus VP1, RNA and non-cytopathic viruses were detected in the stomach biopsy specimens of CFS patients with chronic abdominal complaints.

*

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Chia JK. The role of enterovirus in chronic fatigue syndrome. *J Clin Pathol.* 2005 Nov;58(11):1126-32. PMID: 16254097

Enteroviruses may play a role in CFS.

*

Nairn C, Galbraith DN, Clements GB. Comparison of coxsackie B neutralisation and enteroviral PCR in chronic fatigue patients. *J Med Virol.* 1995 Aug;46(4):310-3. PMID: 7595406

More CFS patients than controls had evidence of enterovirus on a PCR assay.

*

Galbraith DN, Nairn C, Clements GB. Phylogenetic analysis of short enteroviral sequences from patients with chronic fatigue syndrome. *J Gen Virol.* 1995 Jul;76 (Pt 7):1701-7. PMID: 9049375

The research results suggest there is persistence of enterovirus infection in some CFS patients and indicate the presence of distinct novel enterovirus sequences.

*

Clements GB, McGarry F, Nairn C, Galbraith DN. Detection of enterovirus-specific RNA in serum: the relationship to chronic fatigue. *J Med Virol.* 1995 Feb;45(2):156-61. PMID: 7775934

Enteroviral specific sequences were detected in 36 of 88 serum samples from chronic fatigue patients and 3 of 126 healthy individuals.

*

Bowles NE, Bayston TA, Zhang HY, Doyle D, Lane RJ, Cunningham L, Archard LC. Persistence of enterovirus RNA in muscle biopsy samples suggests that some cases of chronic fatigue syndrome result from a previous, inflammatory viral myopathy. *J Med.* 1993;24(2-3):145-60. PMID: 8409778

CFS may be a sequela of a previous inflammatory viral myopathy.

*

Behan PO, Behan WM, Gow JW, Cavanagh H, Gillespie S. Enteroviruses and postviral fatigue syndrome. *Ciba Found Symp.* 1993;173:146-54; discussion 154-9. PMID: 8387908

An increase in the number and size of muscle mitochondria was found in 70% of postviral fatigue cases, suggesting an abnormality in metabolic function. Evidence of hypothalamic dysfunction was present, particularly involving 5-hydroxytryptamine metabolism.

*

Gow JW, Behan WM. Amplification and identification of enteroviral sequences in the postviral fatigue syndrome. *Br Med Bull.* 1991 Oct;47(4):872-85. PMID: 1665380

A highly significant number of muscle biopsies from CFS patients were positive for enteroviral sequences.

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*

Gow JW, Behan WM, Clements GB, Woodall C, Riding M, Behan PO. Enteroviral RNA sequences detected by polymerase chain reaction in muscle of patients with postviral fatigue syndrome. *BMJ*. 1991 Mar 23;302(6778):692-6. PMID: 1850635

Persistent enteroviral infection of muscle may occur in some patients with postviral fatigue syndrome.

*

Cunningham L, Bowles NE, Lane RJ, Dubowitz V, Archard LC. Persistence of enteroviral RNA in chronic fatigue syndrome is associated with the abnormal production of equal amounts of positive and negative strands of enteroviral RNA. *J Gen Virol*. 1990 Jun;71 (Pt 6):1399-402. PMID: 2161907

This study suggests that enterovirus persistence in muscle is due to a defect in control of viral RNA synthesis.

Gut

Frémont M, Coomans D, Massart S, De Meirleir K. High-throughput 16S rRNA gene sequencing reveals alterations of intestinal microbiota in myalgic encephalomyelitis/chronic fatigue syndrome patients. *Anaerobe*. 2013 Aug;22:50-6. PMID: 23791918

These results showed that intestinal microbiota was altered in a group of ME/CFS patients from Belgium and Norway.

*

Lakhan SE, Kirchgessner A. Gut inflammation in chronic fatigue syndrome. *Nutr Metab (Lond)*. 2010 Oct 12;7:79. PMID: 20939923

CFS patients have a variety of gut problems, including mucosal barrier dysfunction ("leaky gut"), an altered mucosal immune system, and presence of various microorganisms related to disease.

*

Sheedy JR, Wettenhall RE, Scanlon D, Gooley PR, Lewis DP, McGregor N, Stapleton DI, Butt HL, De Meirleir KL. Increased d-lactic Acid intestinal bacteria in patients with chronic fatigue syndrome. *In Vivo*. 2009 Jul-Aug;23(4):621-8. PMID: 19567398

CFS patients have abnormal levels of Gram positive facultative anaerobic D-lactic bacteria in their intestinal systems. This has the potential of explaining some of the symptoms and of serving as a biomarker.

*

Frémont M, Metzger K, Rady H, Hulstaert J, De Meirleir K. Detection of herpesviruses and parvovirus B19 in gastric and intestinal mucosa of chronic fatigue syndrome patients. *In Vivo*. 2009 Mar-Apr;23(2):209-13. PMID: 19414405

CFS patients tend to have a variety of pathogenic viruses colonizing their gastrointestinal tracts; these include parvovirus B19, HHV6, HHV7 and EBV.

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*

Maes M, Leunis JC. Normalization of leaky gut in chronic fatigue syndrome (CFS) is accompanied by a clinical improvement: effects of age, duration of illness and the translocation of LPS from gram-negative bacteria. *Neuro Endocrinol Lett.* 2008 Dec;29(6):902-10. PMID: 19112401

CFS patients have high intestinal permeability, and treatment of this can result in improvements in their condition.

*

Maes M, Mihaylova I, Leunis JC. Increased serum IgA and IgM against LPS of enterobacteria in chronic fatigue syndrome (CFS): indication for the involvement of gram-negative enterobacteria in the etiology of CFS and for the presence of an increased gut-intestinal permeability. *J Affect Disord.* 2007 Apr;99(1-3):237-40. PMID: 17007934

Prevalences and median values for serum IgA against the LPS of enterobacteria are significantly greater in patients with CFS than in normal volunteers and patients with partial CFS. Serum IgA levels were significantly correlated to the severity of illness.

*

Maes M, Coucke F, Leunis JC. Normalization of the increased translocation of endotoxin from gram negative enterobacteria (leaky gut) is accompanied by a remission of chronic fatigue syndrome. *Neuro Endocrinol Lett.* 2007 Dec;28(6):739-44. PMID: 18063928

CFS is accompanied by an increased translocation of endotoxins from gram-negative enterobacteria through the gut wall, as demonstrated by increased prevalences and median values for serum IgM and IgA against the endotoxins of gram-negative enterobacteria. This condition can also be described as increased gut permeability or leaky gut. Here, a patient was treated with specific antibiotics and diet to treat gut permeability, as well as intravenous immunoglobins, and went into remissions.

Candida

Evengård B, Gräns H, Wahlund E, Nord CE. Increased number of *Candida albicans* in the faecal microflora of chronic fatigue syndrome patients during the acute phase of illness. *Scand J Gastroenterol.* 2007 Dec;42(12):1514-5. PMID: 17886123

CFS patients have an overgrowth of candida in the intestines.

*

Cater RE 2nd. Chronic intestinal candidiasis as a possible etiological factor in the chronic fatigue syndrome. *Med Hypotheses.* 1995 Jun;44(6):507-15. PMID: 7476598

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It is proposed that chronic intestinal candidiasis may be an agent which leads to immune depression in many CFS patients and therefore that it could be a causal factor in CFS.

Mycoplasma

Endresen GK. Mycoplasma blood infection in chronic fatigue and fibromyalgia syndromes. *Rheumatol Int.* 2003 Sep;23(5):211-5. PMID: 12879275

Mycoplasma blood infection has been detected in about 50% of patients with CFS and/or FMS. Most patients with CFS/FMS who have mycoplasma infection appear to recover and reach their pre-illness state after long-term antibiotic therapy with doxycycline.

*

Nijs J, Nicolson GL, De Becker P, Coomans D, De Meirleir K. High prevalence of Mycoplasma infections among European chronic fatigue syndrome patients. Examination of four Mycoplasma species in blood of chronic fatigue syndrome patients. *FEMS Immunol Med Microbiol.* 2002 Nov 15;34(3):209-14. PMID: 12423773

Compared to American CFS patients (M. pneumoniae>M. hominis>M. penetrans), a slightly different pattern of mycoplasmal infections was found in European CFS patients (M. hominis>M. pneumoniae, M. fermentans>M. penetrans).

*

Nasralla M, Haier J, Nicolson GL. Multiple mycoplasmal infections detected in blood of patients with chronic fatigue syndrome and/or fibromyalgia syndrome. *Eur J Clin Microbiol Infect Dis.* 1999 Dec;18(12):859-65. PMID:10691196

More than 60% of patients with CFS were found to have mycoplasmal blood infections, such as Mycoplasma fermentans infection. More than half the patients had multiple infections.

*

Vojdani A, Choppa PC, Tagle C, Andrin R, Samimi B, Lapp CW. Detection of Mycoplasma genus and Mycoplasma fermentans by PCR in patients with Chronic Fatigue Syndrome. *FEMS Immunol Med Microbiol.* 1998 Dec;22(4):355-65. PMID: 9879928

A polymerase chain reaction (PCR)-based assay was used to detect Mycoplasma genus and M. fermentans genomes in peripheral blood mononuclear cells (PBMC) of CFS patients. Mycoplasma genus and M. fermentans were found in 52% and 24% of CFS samples, vs. 14% and 8% of control subjects (P<0.0001).

*

Choppa PC, Vojdani A, Tagle C, Andrin R, Magtoto L. Multiplex PCR for the detection of Mycoplasma fermentans, M. hominis and M. penetrans in cell cultures and blood samples of patients with chronic fatigue syndrome. *Mol Cell Probes.* 1998 Oct;12(5):301-8. PMID: 9778455

The percentage of Mycoplasma infection was found to be 52% in CFS patients and 15% in healthy individuals. Mycoplasma fermentans, M. hominis and M. penetrans were detected in 32%, 9% and 6% of the CFS patients, compared to 8%, 3% and 2% of the healthy control subjects, respectively.

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Parvovirus B19

Kerr JR, Gough J, Richards SC, Main J, Enlander D, McCreary M, Komaroff AL, Chia JK. Antibody to parvovirus B19 nonstructural protein is associated with chronic arthralgia in patients with chronic fatigue syndrome/myalgic encephalomyelitis. *J Gen Virol.* 2010 Apr;91(Pt 4):893-7. PMID: 20007355

Eighty-three CFS patients (41.5 %) as compared with fourteen (7%) normal blood donors tested positive for anti-B19 NS1 IgG. Of these 83 patients, 61 complained of chronic joint pain, while 22 did not. Parvovirus B19 DNA was detected in serum of 11 CFS patients and none of the controls by Taqman real-time PCR. Positivity for anti-B19 NS1 IgG was associated with higher expression levels of the human CFS-associated genes NHLH1 and GABPA.

*

Seishima M, Mizutani Y, Shibuya Y, Arakawa C. Chronic fatigue syndrome after human parvovirus B19 infection without persistent viremia. *Dermatology.* 2008;216(4):341-6. PMID: 18277075

Some patients who get sick after a parvovirus B19 infection do not show antibodies.

*

Kerr JR. Pathogenesis of parvovirus B19 infection: host gene variability, and possible means and effects of virus persistence. *J Vet Med B Infect Dis Vet Public Health.* 2005 Sep-Oct;52(7-8):335-9. PMID: 16316396

In a study of CFS patients, six genes were found to be differentially expressed with roles in the cytoskeleton (SKIP, MACF1, SPAG7, FLOT1), integrin signalling (FLOT1, RASSF5), HLA class III (c6orf48), and tumour suppression (RASSF5). These results have implications not only for B19 but also for other persistent viruses.

*

Jacobson SK, Daly JS, Thorne GM, McIntosh K. Chronic parvovirus B19 infection resulting in chronic fatigue syndrome: case history and review. *Clin Infect Dis.* 1997 Jun;24(6):1048-51. PMID: 9195056

The authors report the case of a young woman with recurrent fever and a syndrome indistinguishable from chronic fatigue syndrome. After extensive investigation, they found persistent parvovirus B19 viremia, which was detectable by polymerase chain reaction (PCR) despite the presence of IgM and IgG antibodies to parvovirus B19. The patient's fever resolved with the administration of intravenous immunoglobulin.

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Coxiella Burnetii

Strauss B, Löschau M, Seidel T, Stallmach A, Thomas A. Are fatigue symptoms and chronic fatigue syndrome following Q fever infection related to psychosocial variables? *J Psychosom Res.* 2012 Apr;72(4):300-4. PMID: 22405225

Although in the researchers' sample fatigue symptoms were common among Q fever patients, they found no increased prevalence of CFS in contrast to several other studies.

*

Ledina D, Bradarić N, Milas I, Ivić I, Brncić N, Kuzmicić N. Chronic fatigue syndrome after Q fever. *Med Sci Monit.* 2007 Jul;13(7):CS88-92. PMID: 17599032

Coxiella burnetii infection may be involved in the evolution of CFS.

*

Iwakami E, Arashima Y, Kato K, Komiya T, Matsukawa Y, Ikeda T, Arakawa Y, Oshida S. Treatment of chronic fatigue syndrome with antibiotics: pilot study assessing the involvement of *Coxiella burnetii* infection. *Intern Med.* 2005 Dec;44(12):1258-63. PMID: 16415546

Four CFS patients (the CFS group) and 54 controls [the post-Q fever fatigue syndrome (QFS) group] positive for *C. burnetii* were treated mainly with minocycline or doxycycline (100 mg/day) for 3 months. After treatment, all 58 patients tested negative for *C. burnetii* infection. In the CFS group, health did not improve.

*

Ayres JG, Flint N, Smith EG, Tunnicliffe WS, Fletcher TJ, Hammond K, Ward D, Marmion BP. Post-infection fatigue syndrome following Q fever. *QJM.* 1998 Feb;91(2):105-23. PMID: 9578893

The authors looked at a group of people who were infected with Q fever in 1989, finding CFS in 42.3% of cases and 26% of controls.

Borna Disease

Nakaya T, Kuratsune H, Kitani T, Ikuta K. Demonstration on Borna disease virus in patients with chronic fatigue syndrome. *Nihon Rinsho.* 1997 Nov;55(11):3064-71. PMID: 9396313

In Japanese patients with CFS, the prevalence of Borna disease virus infection was 34% (30/89) and 12% (7/57) by immunoblotting and PCR analysis, respectively. Furthermore, anti-BDV antibodies and BDV RNA were detected in a family cluster with CFS. These results suggested that this virus contributes to or initiates CFS, although the single etiologic role of BDV is unlikely.

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Nakaya T, Takahashi H, Nakamura Y, Asahi S, Tobiume M, Kuratsune H, Kitani T, Yamanishi K, Ikuta K. Demonstration of Borna disease virus RNA in peripheral blood mononuclear cells derived from Japanese patients with chronic fatigue syndrome. FEBS Lett. 1996 Jan 8;378(2):145-9. PMID: 8549821

Laboratory analysis suggests that there is a prevalence of 32% of Borna disease virus in Japanese CFS patients.

Stealth Virus

Martin WJ. Genetic instability and fragmentation of a stealth viral genome. Pathobiology. 1996;64(1):9-17. PMID: 8856790

Partial sequencing was performed on cloned DNA obtained from cultures of a stealth virus isolated from a patient with the chronic fatigue syndrome. The results extend earlier findings showing regions of homology to cytomegalovirus (CMV).

*

Martin WJ. Severe stealth virus encephalopathy following chronic-fatigue-syndrome-like illness: clinical and histopathological features. Pathobiology. 1996;64(1):1-8. PMID: 8856789

The clinical histories and brain biopsy findings of 3 patients with severe stealth virus encephalopathy are reviewed.

*

Martin WJ, Ahmed KN, Zeng LC, Olsen JC, Seward JG, Seehrai JS. African green monkey origin of the atypical cytopathic 'stealth virus' isolated from a patient with chronic fatigue syndrome. Clin Diagn Virol. 1995 Jul;4(1):93-103. PMID: 15566831

The findings implicate an African green monkey as the probable source of the "stealth" virus isolated from this CFS patient.

*

Martin WJ, Glass RT. Acute encephalopathy induced in cats with a stealth virus isolated from a patient with chronic fatigue syndrome. Pathobiology. 1995;63(3):115-8. PMID: 8821627

A simian cytomegalovirus-related stealth virus, isolated from a patient with the chronic fatigue syndrome, induced an acute neurological illness when inoculated into cats.

*

Martin WJ, Zeng LC, Ahmed K, Roy M. Cytomegalovirus-related sequence in an atypical cytopathic virus repeatedly isolated from a patient with chronic fatigue syndrome. Am J Pathol. 1994 Aug;145(2):440-51. PMID: 8053501

The authors describe a novel type of CMV-related "stealth" virus that is able to establish a clinically

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persistent human infection.

Other Infections

Elfaitouri A, Herrmann B, Bölin-Wiener A, Wang Y, Gottfries CG, Zachrisson O, Pipkorn R, Rönnblom L, Blomberg J. Epitopes of microbial and human heat shock protein 60 and their recognition in myalgic encephalomyelitis. *PLoS One*. 2013 Nov 28;8(11):e81155. PMID: 24312270

A peptide from *Chlamydia pneumoniae* human heat shock protein was detected in 24% of ME samples compared to less than 1% of non-ME samples (taken from blood donor, multiple sclerosis patients and systemic lupus erythematosus patients).

*

Mørch K, Hanevik K, Rivenes AC, Bødtker JE, Næss H, Stubhaug B, Wensaas KA, Rortveit G, Eide GE, Hausken T, Langeland N. Chronic fatigue syndrome 5 years after giardiasis: differential diagnoses, characteristics and natural course. *BMC Gastroenterol*. 2013 Feb 12;13:28. PMID:23399438

A high prevalence of chronic fatigue has previously been reported following giardiasis after a large waterborne outbreak in Bergen, Norway in 2004. This study shows that *Giardia duodenalis* may induce CFS persisting as long as five years after the infection.

*

Hanevik K, Kristoffersen EK, Sørnes S, Mørch K, Næss H, Rivenes AC, Bødtker JE, Hausken T, Langeland N. Immunophenotyping in post-giardiasis functional gastrointestinal disease and chronic fatigue syndrome. *BMC Infect Dis*. 2012 Oct 14;12:258. PMID: 23061432

A *Giardia* outbreak was associated with development of post-infectious functional gastrointestinal disorders (PI-FGID) and chronic fatigue syndrome (PI-CFS). Five years later, researchers found significantly higher CD8 T-cell levels in PI-FGID, and significantly lower NK-cell levels in PI-CFS patients. Severity of abdominal and fatigue symptoms correlated negatively with NK-cell levels.

*

Naess H, Nyland M, Hausken T, Follestad I, Nyland HI. Chronic fatigue syndrome after *Giardia* enteritis: clinical characteristics, disability and long-term sickness absence. *BMC Gastroenterol*. 2012 Feb 8;12:13. PMID: 22316329

After a giardiasis enteritis outbreak, at least 5% of those affected developed clinical characteristics and functional impairment comparable to previously described post-infectious fatigue syndrome.

*

Larbcharoensub N, Boonsakan P, Aroonroch R, Rochanawutanon M, Nitiyanant P, Phongkitkarun S, Poonvutikul S, Watcharananan SP, Ngarmukos C. Adrenal histoplasmosis: a case series and review of the literature. *Southeast Asian J Trop Med Public Health*. 2011 Jul;42(4):920-5. PMID: 22299474

The authors report seven cases of adrenal histoplasmosis in immunocompetent patients. All patients

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presented as chronic fatigue syndrome. The onset of symptoms ranged from one to three months. A cure was accomplished in 6 out of 7 cases.

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Maes M, Twisk FN, Kubera M, Ringel K, Leunis JC, Geffard M. Increased IgA responses to the LPS of commensal bacteria is associated with inflammation and activation of cell-mediated immunity in chronic fatigue syndrome. *J Affect Disord.* 2011 Oct 1. PMID: 21967891

Increased IgA responses to commensal bacteria in ME/CFS are associated with inflammation and cell-mediated immunity activation, which are associated with symptom severity. It is concluded that increased translocation of commensal bacteria may be responsible for the disease activity in some ME/CFS patients.

*

Grinde B. Is chronic fatigue syndrome caused by a rare brain infection of a common, normally benign virus? *Med Hypotheses.* 2008 Aug;71(2):270-4. PMID: 18440157

The authors propose that CFS is caused by a circovirus.

*

Sairenji T, Nagata K. Viral infections in chronic fatigue syndrome. *Nihon Rinsho.* 2007 Jun;65(6):991-6. PMID: 17561687

The major hypothesis of the pathogenesis of CFS is that infectious agents such as viruses, may trigger and lead to chronic activation of the immune system with abnormal regulation of cytokine production. The authors summarize the recent progressive literature of virus, rickettsia, and mycoplasma implicated in the pathogenesis of CFS.

*

Hickie I, Davenport T, Wakefield D, Vollmer-Conna U, Cameron B, Vernon SD, Reeves WC, Lloyd A; Dubbo Infection Outcomes Study Group. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *BMJ.* 2006 Sep 16;333(7568):575. PMID: 16950834

A significant minority of people with variety of infections (including Epstein-Barr virus, Coxiella burnetii or Ross River virus) remain ill with a post-infection syndrome qualifying as CFS over the long term.

*

Jones JF, Kulkarni PS, Butera ST, Reeves WC. GB virus-C--a virus without a disease: we cannot give it chronic fatigue syndrome. *BMC Infect Dis.* 2005 Sep 28;5:78. PMID: 16191201

GB virus-C (GBV-C) virus is a flavivirus with cell tropism and host defense induction qualities compatible with a role in producing the syndrome. The authors found no evidence that active or past infection with GBV is associated with CFS.

*

Ikuta K, Yamada T, Shimomura T, Kuratsune H, Kawahara R, Ikawa S, Ohnishi E, Sokawa Y, Fukushi H, Hirai K, Watanabe Y, Kurata T, Kitani T, Sairenji T. Diagnostic evaluation of 2', 5'-oligoadenylate synthetase activities and antibodies against Epstein-Barr virus and Coxiella burnetii in patients with

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chronic fatigue syndrome in Japan. *Microbes Infect.* 2003 Oct;5(12):1096-102. PMID: 14554250

Some CFS patients may be associated with EBV or *C. burnetii* infection. The up-regulation of 2-5AS activities suggests immunological dysfunctions with some virus infections in the CFS patients.

*

Nicolson GL, Gan R, Haier J. Multiple co-infections (*Mycoplasma*, *Chlamydia*, human herpes virus-6) in blood of chronic fatigue syndrome patients: association with signs and symptoms. *APMIS.* 2003 May;111(5):557-66. PMID: 12887507

A large subset of CFS patients show evidence of bacterial and/or viral infection(s), and these infections may contribute to the severity of signs and symptoms found in these patients.

*

Chia JK, Chia LY. Chronic *Chlamydia pneumoniae* infection: a treatable cause of chronic fatigue syndrome. *Clin Infect Dis.* 1999 Aug;29(2):452-3. PMID: 10476765

Chlamydia pneumoniae is discussed as a contributor to CFS.

*

Pamphlett R, O'Donoghue P. Antibodies against *Sarcocystis* and *Toxoplasma* in humans with the chronic fatigue syndrome. *Aust N Z J Med.* 1992 Jun;22(3):307-8. PMID: 1497558

*

Komaroff AL, Wang SP, Lee J, Grayston JT. No association of chronic *Chlamydia pneumoniae* infection with chronic fatigue syndrome. *J Infect Dis.* 1992 Jan;165(1):184. PMID: 1727893

Endocrine System

Nijhof SL1, Rutten JM2, Uiterwaal CS3, Bleijenberg G4, Kimpen JL5, Putte EM6. The role of hypocortisolism in chronic fatigue syndrome. *Psychoneuroendocrinology.* 2014 Apr;42:199-206. PMID: 24636516

Pre-treatment salivary cortisol levels were significantly lower in CFS patients than in healthy controls. The hypocortisolism found in CFS patients was significantly correlated to the amount of sleep.

*

Powell DJ, Liossi C, Moss-Morris R, Schlotz W. Unstimulated cortisol secretory activity in everyday life and its relationship with fatigue and chronic fatigue syndrome: A systematic review and subset meta-analysis. *Psychoneuroendocrinology.* 2013 Nov;38(11):2405-22. PMID: 23916911

Meta-analyses revealed an attenuation of the cortisol-awakening response increase within CFS compared to controls but no statistically significant differences between groups for other markers.

*

Aschbacher K, Adam EK, Crofford LJ, Kemeny ME, Demitrack MA, Ben-Zvi A. Linking disease symptoms

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and subtypes with personalized systems-based phenotypes: a proof of concept study. *Brain Behav Immun.* 2012 Oct;26(7):1047-56. PMID: 22687333

A dynamic systems model was used to generate parameters describing a phenotype of Hypothalamic-Pituitary-Adrenal (HPA) behavior in a sample of 36 patients with chronic fatigue syndrome (CFS) and/or fibromyalgia (FM) and 36 case-matched healthy controls.

*

Papadopoulos AS, Cleare AJ. Hypothalamic-pituitary-adrenal axis dysfunction in chronic fatigue syndrome. *Nat Rev Endocrinol.* 2011 Sep 27. PMID: 21946893

The weight of current evidence supports the presence of the following factors related to hypothalamic-pituitary-adrenal (HPA) axis dysfunction in patients with chronic fatigue syndrome (CFS): mild hypocortisolism; attenuated diurnal variation of cortisol; enhanced negative feedback to the HPA axis; and blunted HPA axis responsiveness.

*

Ursini F, Succurro E, Grembiale A, Gagliardi DA, Arturi F. The HPA axis in the pathogenesis of chronic fatigue syndrome. *Clin Ter.* 2010 Sep-Oct;161(5):461-4. PMID: 20949245

A review of evidence about a role of hypothalamic-pituitary-adrenal axis in the pathogenesis of CFS.

*

Shishioh-Ikejima N, Ogawa T, Yamaguti K, Watanabe Y, Kuratsune H, Kiyama H. The increase of alpha-melanocyte-stimulating hormone in the plasma of chronic fatigue syndrome patients. *BMC Neurol.* 2010 Aug 23;10:73. PMID: 20731841

CFS patients with a disease duration of ≤ 5 years had significantly higher levels of alpha-MSH in their peripheral blood, and this has potential as a biomarker.

*

Wyller VB, Evang JA, Godang K, Solhjell KK, Bollerslev J. Hormonal alterations in adolescent chronic fatigue syndrome. *Acta Paediatr.* 2010 May;99(5):770-3. PMID:20199497

Among CFS patients, plasma antidiuretic hormone was significantly decreased and serum osmolality and plasma renin activity were significantly increased ($p \leq 0.001$). Serum concentration of aldosterone, cortisol, NT-proBNP and sex hormones were not significantly different in the two groups.

*

Fomicheva EE, Filatenkova TA, Rybakina EG. Activity in the hypothalamo-hypophyseal- adrenocortical system on experimental induction of chronic fatigue syndrome. *Neurosci Behav Physiol.* 2010 Mar;40(3):245-50. PMID: 20146018

In an experimental model, CFS was associated with abnormalities in adrenal function.

*

Weaver SA, Janal MN, Aktan N, Ottenweller JE, Natelson BH. Sex differences in plasma prolactin response to tryptophan in chronic fatigue syndrome patients with and without comorbid fibromyalgia. *J Womens*

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Health (Larchmt). 2010 May;19(5):951-8. PMID: 20384451

Women with CFS alone, but not CFS plus fibromyalgia, showed upregulated plasma prolactin responses compared with controls. There were no differences among groups of men.

*

Evans KM, Flanagan DE, Wilkin TJ. Chronic fatigue: is it endocrinology? Clin Med. 2009 Feb;9(1):34-8. PMID: 19271598

CFS patients' presenting symptoms are not early features of "significant endocrine pathology."

*

Rybakina EG, Shanin SN, Fomicheva EE, Korneva EA. Cellular and molecular mechanisms of interaction between the neuroendocrine and immune systems under chronic fatigue syndrome in experiment. Ross Fiziol Zh Im I M Sechenova. 2009 Dec;95(12):1324-35. PMID: 20141043

In an experimental model, CFS was associated with alterations in HPA axis activity. This likely results in changes in both the activity of immune-competent cells and membranes of brain cells.

*

Fomicheva EE, Filatenkova TA, Rybakina EG. Activity of hypothalamic-pituitary-adrenal axis by induction of experimental chronic fatigue syndrome. Ross Fiziol Zh Im I M Sechenova. 2009 Jan;95(1):11-8. PMID: 19323439

CFS patients display disordered HPA axis and adrenal functioning.

*

Van Houdenhove B, Van Den Eede F, Luyten P. Does hypothalamic-pituitary-adrenal axis hypofunction in chronic fatigue syndrome reflect a 'crash' in the stress system? Med Hypotheses. 2009 Jun;72(6):701-5. PMID: 19237251

The authors hypothesize that that HPA axis hypofunction in CFS, conceptualized within a system-biological perspective, primarily reflects a fundamental and persistent dysregulation of the neurobiological stress system.

*

Veldman J, Van Houdenhove B, Verguts J. Chronic fatigue syndrome: a hormonal origin? A rare case of dysmenorrhea membranacea. Arch Gynecol Obstet. 2009 May;279(5):717-20. PMID: 18787800

A case study of involving membranous dysmenorrhea suggests a hormonal dysfunction as a possible cause of CFS.

*

Papadopoulos A, Ebrecht M, Roberts AD, Poon L, Rohleder N, Cleare AJ. Glucocorticoid receptor mediated negative feedback in chronic fatigue syndrome using the low dose (0.5 mg) dexamethasone suppression test. J Affect Disord. 2009 Jan;112(1- 3):289-94. PMID: 18573538

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A low-dose dexamethasone (0.5 mg) suppression test in CFS patients showed no differences with controls except in the patients who also were depressed.

*

Fuite J, Vernon SD, Broderick G. Neuroendocrine and immune network re-modeling in chronic fatigue syndrome: an exploratory analysis. *Genomics*. 2008 Dec;92(6):393-9. PMID: 18775774

This work investigates the significance of changes in association patterns linking indicators of neuroendocrine and immune activity in patients with CFS. Findings align with known mechanisms of chronic inflammation and support possible immune-mediated loss of thyroid function in CFS exacerbated by blunted HPA axis responsiveness.

*

Torres-Harding S, Sorenson M, Jason L, Maher K, Fletcher MA, Reynolds N, Brown M. The associations between basal salivary cortisol and illness symptomatology in chronic fatigue syndrome. *J Appl Biobehav Res*. 2008 Jan 1;13:157-180. PMID: 19701493

CFS patients show deviations from expected patterns of cortisol, and this appears to be associated with fatigue and pain.

*

Nater UM, Maloney E, Boneva RS, Gurbaxani BM, Lin JM, Jones JF, Reeves WC, Heim C. Attenuated morning salivary cortisol concentrations in a population-based study of persons with chronic fatigue syndrome and well controls. *J Clin Endocrinol Metab*. 2008 Mar;93(3):703-9. PMID: 18160468

CFS was associated with an attenuated morning cortisol response, but the effect was limited to women.

*

Van Den Eede F, Moorkens G, Hulstijn W, Van Houdenhove B, Cosyns P, Sabbe BG, Claes SJ. Combined dexamethasone/corticotropin-releasing factor test in chronic fatigue syndrome. *Psychol Med*. 2008 Jul;38(7):963-73. PMID: 17803834

CFS is globally associated with reduced cortisol responses in the combined low-dose Dex/CRF test, but this effect is only clearly present in CFS patients without a history of early-life stress.

*

Van Den Eede F, Moorkens G, Van Houdenhove B, Cosyns P, Claes SJ. Hypothalamic-pituitary-adrenal axis function in chronic fatigue syndrome. *Neuropsychobiology*. 2007;55(2):112-20. PMID: 17596739

Hypofunction of the hypothalamic-pituitary-adrenal (HPA) axis is a problem in a proportion of the patients with CFS, possibly as a consequence of other factors.

*

Jerjes WK, Taylor NF, Wood PJ, Cleare AJ. Enhanced feedback sensitivity to prednisolone in chronic fatigue syndrome. *Psychoneuroendocrinology*. 2007 Feb;32(2):192-8. PMID: 17276605

There is enhanced sensitivity of the HPA axis to negative feedback in CFS.

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*

Gräns H, Nilsson M, Dahlman-Wright K, Evengård B. Reduced levels of oestrogen receptor beta mRNA in Swedish patients with chronic fatigue syndrome. *J Clin Pathol.* 2007 Feb;60(2):195-8. PMID: 16731592

The CFS group showed significantly lower mRNA expression levels of ERbeta wt compared with the healthy control group. This is consistent with an immune-mediated pathogenesis of CFS. A possible connection between oestrogen, oestrogen receptors and CFS should be evaluated further.

*

Tanriverdi F, Karaca Z, Unluhizarci K, Kelestimur F. The hypothalamo-pituitary-adrenal axis in chronic fatigue syndrome and fibromyalgia syndrome. *Stress.* 2007 Mar;10(1):13- 25. PMID: 17454963

The role of the hypothalamo-pituitary-adrenal (HPA) axis in CFS is discussed.

*

Maloney EM, Gurbaxani BM, Jones JF, de Souza Coelho L, Pennachin C, Goertzel BN. Chronic fatigue syndrome and high allostatic load. *Pharmacogenomics.* 2006 Apr;7(3):467-73. PMID: 16610956

CFS was associated with a high level of allostatic load. The three allostatic load components that best discriminated cases from controls were waist:hip ratio, aldosterone and urinary cortisol.

*

Maes M, Mihaylova I, De Ruyter M. Decreased dehydroepiandrosterone sulfate but normal insulin-like growth factor in chronic fatigue syndrome (CFS): relevance for the inflammatory response in CFS. *Neuro Endocrinol Lett.* 2005 Oct;26(5):487-92. PMID: 16264414

CFS is accompanied by lowered levels of DHEAS, and this may play a role in the immune (defect in the early activation of T cells) and the inflammatory pathophysiology of CFS.

*

Segal TY, Hindmarsh PC, Viner RM. Disturbed adrenal function in adolescents with chronic fatigue syndrome. *J Pediatr Endocrinol Metab.* 2005 Mar;18(3):295-301. PMID: 15813608

Adolescents with CFS have subtle alterations in adrenal function suggesting a reduction in central stimulation of the adrenal glands

*

Di Giorgio A, Hudson M, Jerjes W, Cleare AJ. 24-hour pituitary and adrenal hormone profiles in chronic fatigue syndrome. *Psychosom Med.* 2005 May-Jun;67(3):433-40. PMID: 15911907

Patients with CFS demonstrated subtle alterations in HPA axis activity characterized by reduced ACTH over a full circadian cycle and reduced levels during the usual morning physiological peak ACTH secretion. This provides evidence of subtle dysregulation of the HPA axis in CFS.

*

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Crofford LJ, Young EA, Engleberg NC, Korszun A, Brucksch CB, McClure LA, Basal circadian and pulsatile ACTH and cortisol secretion in patients with fibromyalgia and/or chronic fatigue syndrome. *Brain Behav Immun.* 2004 Jul;18(4):314-25. PMID: 15157948

CFS patients, fibromyalgia patients and normal controls all look different in their basal circadian architecture of HPA axis hormones.

*

Cevik R, Gur A, Acar S, Nas K, Sarac AJ. Hypothalamic-pituitary-gonadal axis hormones and cortisol in both menstrual phases of women with chronic fatigue syndrome and effect of depressive mood on these hormones. *BMC Musculoskelet Disord.* 2004 Dec 8;5:47. PMID: 15588275

There were no significant differences in FSH, LH, estradiol and progesterone levels in both of menstrual phases of CFS patients versus controls. Cortisol levels were significantly lower in patients compared to controls.

*

Gaab J, Engert V, Heitz V, Schad T, Schürmeyer TH, Ehlert U. Associations between neuroendocrine responses to the Insulin Tolerance Test and patient characteristics in chronic fatigue syndrome. *J Psychosom Res.* 2004 Apr;56(4):419-24. PMID: 15094026

CFS patients had a significantly reduced area under the ACTH response curve (AUC) in the ITT. The AUC was significantly associated with the duration of CFS symptoms and the severity of fatigue symptomatology. In addition, duration of CFS was correlated with the severity of fatigue symptoms.

*

Zarković M, Pavlović M, Pokrajac-Simeunović A, Cirić J, Beleslin B, Penezić Z, Ognjanović S, Savić S, Poluga J, Trbojević B, Drezgić M. Disorder of adrenal gland function in chronic fatigue syndrome. *Srp Arh Celok Lek.* 2003 Sep-Oct;131(9-10) 370-4. PMID: 15058215

Regarding the adrenal response to ACTH stimulation CFS subjects present heterogeneous group. In some subjects cortisol response is preserved, while in the others it is similar to one found in secondary adrenal insufficiency.

*

Murphy BE, Abbott FV, Allison CM, Watts C, Ghadirian AM. Elevated levels of some neuroactive progesterone metabolites, particularly isopregnanolone, in women with chronic fatigue syndrome. *Psychoneuroendocrinology.* 2004 Feb;29(2):245-68. PMID: 14604604

Increases in ring A-reduced progesterone metabolites, particularly isopregnanolone, are associated with CFS. The pathophysiology of CFS is unlikely to be due to depression.

*

Gaab J, Hüster D, Peisen R, Engert V, Heitz V, Schad T, Schürmeyer T, Ehlert U. Assessment of cortisol response with low-dose and high-dose ACTH in patients with

chronic fatigue syndrome and healthy comparison subjects. *Psychosomatics.* 2003 Mar- Apr;44(2):113-9. PMID: 12618533

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No response differences for salivary and plasma cortisol were detectable after administration of either low-dose or high-dose ACTH for CFS patients vs. controls, indicating that primary adrenal insufficiency is unlikely to play a significant role in the etiology of chronic fatigue syndrome.

*

Gaab J, Hüster D, Peisen R, Engert V, Heitz V, Schad T, Schürmeyer TH, Ehlert U. Hypothalamic-pituitary-adrenal axis reactivity in chronic fatigue syndrome and health under psychological, physiological, and pharmacological stimulation. *Psychosom Med.* 2002 Nov-Dec;64(6):951-62. PMID: 12461200

CFS patients seem capable of mounting a sufficient cortisol response under different types of stress, but on a central level subtle dysregulations of the HPA axis exist.

*

Racciatti D, Guagnano MT, Vecchiet J, De Remigis PL, Pizzigallo E, Della Vecchia R, Di Sciascio T, Merlitti D, Sensi S. Chronic fatigue syndrome: circadian rhythm and hypothalamic-pituitary-adrenal (HPA) axis impairment. *Int J Immunopathol Pharmacol.* 2001 Jan-Apr;14(1):11-15. PMID: 12622884

The circadian rhythms of prolactin, thyrotropic hormone, adrenocorticotrophic hormone and cortisol were statistically significant in both CFS and control groups.

*

van Rensburg SJ, Potocnik FC, Kiss T, Hugo F, van Zijl P, Mansvelt E, Carstens ME, Theodorou P, Hurly PR, Emsley RA, Taljaard JJ. Serum concentrations of some metals and steroids in patients with chronic fatigue syndrome with reference to neurological and cognitive abnormalities. *Brain Res Bull.* 2001 May 15;55(2):319-25. PMID: 11470334

CFS patients had significantly increased serum aluminum and decreased iron compared to controls. In the females, serum iron and dehydroepiandrosterone sulphate were significantly decreased and correlated. Total cholesterol was significantly increased, and significantly negatively correlated with dehydroepiandrosterone sulphate. There were no differences in zinc, copper, cortisol, hemoglobin, transferrin and ferritin concentrations, or in transferrin genetic subtypes.

*

Vassallo CM, Feldman E, Peto T, Castell L, Sharpley AL, Cowen PJ. Decreased tryptophan availability but normal post-synaptic 5-HT_{2c} receptor sensitivity in chronic fatigue syndrome. *Psychol Med.* 2001 May;31(4):585-91. PMID: 11352361

Chronic fatigue syndrome (CFS) has been associated with increased prolactin (PRL) responses to the serotonin (5-HT) releasing agent fenfluramine. The sensitivity of post-synaptic 5-HT_{2c} receptors was not increased in patients with CFS. This suggests that the increased PRL response to fenfluramine in CFS is due to elevated activity of pre-synaptic 5-HT neurones.

*

Visser J, Lentjes E, Haspels I, Graffelman W, Blauw B, de Kloet R, Nagelkerken L. Increased sensitivity to glucocorticoids in peripheral blood mononuclear cells of chronic fatigue syndrome patients, without evidence for altered density or affinity of glucocorticoid receptors. *J Investig Med.* 2001 Mar;49(2):195-204. PMID: 11288761

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In conclusion, peripheral blood mononuclear cells of CFS patients display an increased sensitivity to glucocorticoids.

*

Cleare AJ, Blair D, Chambers S, Wessely S. Urinary free cortisol in chronic fatigue syndrome. *Am J Psychiatry*. 2001 Apr;158(4):641-3. PMID: 11282703

There is mild hypocortisolism in chronic fatigue syndrome.

*

Visser JT, De Kloet ER, Nagelkerken L. Altered glucocorticoid regulation of the immune response in the chronic fatigue syndrome. *Ann N Y Acad Sci*. 2000;917:868-75. PMID: 11268418

In CFS patients a decreased Th1/Th2 balance may be the result of selective effects of glucocorticoids on the IL-10/IL-12 regulatory circuit.

*

Otteweller JE, Sisto SA, McCarty RC, Natelson BH. Hormonal responses to exercise in chronic fatigue syndrome. *Neuropsychobiology*. 2001 Jan;43(1):34-41. PMID: 11150897

The authors looked at endocrine measures in CFS patients before and after an exercise challenge, and conclude that post-exertional malaise is not the result of endocrine problems.

*

Torpy DJ, Bachmann AW, Grice JE, Fitzgerald SP, Phillips PJ, Whitworth JA, Jackson RV. Familial corticosteroid-binding globulin deficiency due to a novel null mutation: association with fatigue and relative hypotension. *J Clin Endocrinol Metab*. 2001 Aug;86(8):3692-700. PMID: 11502797

The authors describe a 39-member Italian-Australian family with a novel complete loss of function (null) mutation of the corticosteroid-binding globulin gene. Idiopathic chronic fatigue was present in 12 of 14 adult null heterozygote subjects (86%) and in 2 of 3 null homozygotes. Five cases met the Centers for Disease Control criteria for chronic fatigue syndrome.

*

Altemus M, Dale JK, Michelson D, Demitrack MA, Gold PW, Straus SE. Abnormalities in response to vasopressin infusion in chronic fatigue syndrome. *Psychoneuroendocrinology*. 2001 Feb;26(2):175-88. PMID: 11087963

Patients with chronic fatigue syndrome had a reduced ACTH response to a vasopressin infusion and a more rapid cortisol response to the infusion.

*

Scott LV, Svec F, Dinan T. A preliminary study of dehydroepiandrosterone response to low-dose ACTH in chronic fatigue syndrome and in healthy subjects. *Psychiatry Res*. 2000 Dec 4;97(1):21-8. PMID: 11104854

ACTH significantly elevates DHEA levels, with no difference in output between CFS and healthy subjects.

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The DHEA/cortisol ratio decreased in response to ACTH stimulation in healthy subjects but not in the CFS cohort. We suggest this divergence of response between the two groups represents an imbalance in the relative synthetic pathways of the CFS group which, if present chronically and if comparable to daily stressors, may manifest itself as an inappropriate response to stress.

*

Starr A, Scalise A, Gordon R, Michalewski HJ, Caramia MD. Motor cortex excitability in chronic fatigue syndrome. *Clin Neurophysiol.* 2000 Nov;111(11):2025-31. PMID: 11068238

Individuals with CFS do not show the normal fluctuations of motor cortical excitability that accompany and follow non-fatiguing repetitive bimanual finger movements.

*

Knook L, Kavelaars A, Sinnema G, Kuis W, Heijnen CJ. High nocturnal melatonin in adolescents with chronic fatigue syndrome. *J Clin Endocrinol Metab.* 2000 Oct;85(10):3690-2. PMID: 11061525

Nocturnal saliva melatonin levels were significantly higher in CFS patients, compared with controls, at midnight, 0100 h, and 0200 h ($P < 0.001$).

*

Berwaerts J, Moorkens G, Abs R. Secretion of growth hormone in patients with chronic fatigue syndrome. *Growth Horm IGF Res.* 1998 Apr;8 Suppl B:127-9. PMID: 10990147

CFS patients have a tendency for impaired spontaneous nocturnal GH secretion.

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*

Moorkens G, Berwaerts J, Wynants H, Abs R. Characterization of pituitary function with emphasis on GH secretion in the chronic fatigue syndrome. *Clin Endocrinol (Oxf).* 2000 Jul;53(1):99-106. PMID: 10931086

There was a significant impairment of GH response during insulin-induced hypoglycaemia and a low nocturnal GH secretion in CFS patients. These changes did, however, not lead to different concentrations in serum IGF-I. Significantly increased prolactin and TSH levels were found when compared to controls.

*

Scott LV, Teh J, Reznick R, Martin A, Sohaib A, Dinan TG. Small adrenal glands in chronic fatigue syndrome: a preliminary computer tomography study. *Psychoneuroendocrinology.* 1999 Oct;24(7):759-68. PMID: 10451910

Adrenal gland size was reduced by over 50% in CFS patients, indicative of significant adrenal atrophy.

*

Scott LV, Salahuddin F, Cooney J, Svec F, Dinan TG. Differences in adrenal steroid profile in chronic fatigue syndrome, in depression and in health. *J Affect Disord.* 1999 Jul;54(1-2):129-37. PMID: 10403156

DHEA and DHEA-S levels were significantly lower in the CFS compared to the healthy group. A potential role for DHEA, both therapeutically and as a diagnostic tool, in CFS, is suggested.

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Scott LV, Medbak S, Dinan TG. Desmopressin augments pituitary-adrenal responsivity to corticotropin-releasing hormone in subjects with chronic fatigue syndrome and in healthy volunteers. *Biol Psychiatry*. 1999 Jun 1;45(11):1447-54. PMID: 10356627

Desmopressin was capable of normalizing the pituitary-adrenal response to corticotropin-releasing hormone in CFS patients; this suggests there may be increased vasopressinergic responsivity of the anterior pituitary in CFS and/or that desmopressin may be exerting an effect at an adrenal level.

*

De Becker P, De Meirleir K, Joos E, Campine I, Van Steenberge E, Smits J, Velkeniers B. Dehydroepiandrosterone (DHEA) response to i.v. ACTH in patients with chronic fatigue syndrome. *Horm Metab Res*. 1999 Jan;31(1):18-21. PMID: 10077344

CFS patients in this study had normal basal DHEA levels, but a blunted serum DHEA response curve to i.v. ACTH injection.

*

Kuratsune H, Yamaguti K, Sawada M, Kodate S, Machii T, Kanakura Y, Kitani T. Dehydroepiandrosterone sulfate deficiency in chronic fatigue syndrome. *Int J Mol Med*. 1998 Jan;1(1):143-6. PMID: 9852212

The majority of Japanese patients with CFS had a serum dehydroepiandrosterone sulfate (DHEA-S) deficiency, possibly related to phenomena such as memory, stress, anxiety, sleep and depression.

*

Scott LV, Medbak S, Dinan TG. The low dose ACTH test in chronic fatigue syndrome and in health. *Clin Endocrinol (Oxf)*. 1998 Jun;48(6):733-7. PMID: 9713562

This study provides evidence for a subtle pituitary-adrenal insufficiency in subjects with chronic fatigue syndrome compared to healthy volunteers.

*

Cannon JG, Angel JB, Abad LW, O'Grady J, Lundgren N, Fagioli L, Komaroff AL. Hormonal influences on stress-induced neutrophil mobilization in health and chronic fatigue syndrome. *J Clin Immunol*. 1998 Jul;18(4):291-8. PMID: 9710746

The results of this study suggest that normal endocrine influences on the circulating neutrophil pool may be disrupted in patients with CFS.

*

Peroutka SJ. Chronic fatigue disorders: an inappropriate response to arginine vasopressin? *Med Hypotheses*. 1998 Jun;50(6):521-3. PMID: 9710328

Altered water metabolism resulting from inappropriate release and/or response to arginine vasopressin (AVP) is proposed as a pathophysiological basis of certain chronic fatigue disorders.

*

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Scott LV, Medbak S, Dinan TG. Blunted adrenocorticotropin and cortisol responses to corticotropin-releasing hormone stimulation in chronic fatigue syndrome. *Acta Psychiatr Scand.* 1998 Jun;97(6):450-7. PMID: 9669518

The release of ACTH was significantly attenuated in a group of CFS patients ($P < 0.005$), as was the release of cortisol.

*

Demitrack MA, Crofford LJ. Evidence for and pathophysiologic implications of hypothalamic-pituitary-adrenal axis dysregulation in fibromyalgia and chronic fatigue syndrome. *Ann N Y Acad Sci.* 1998 May 1;840:684-97. PMID: 9629295

The authors studied the detailed, pulsatile characteristics of the HPA axis in a group of CFS patients. Results were consistent with the view that patients with CFS have a reduction of HPA axis activity due, in part, to impaired central nervous system drive.

*

Scott LV, Burnett F, Medbak S, Dinan TG. Naloxone-mediated activation of the hypothalamic-pituitary-adrenal axis in chronic fatigue syndrome. *Psychol Med.* 1998 Mar;28(2):285-93. PMID: 9572086

The release of ACTH (but not cortisol) was significantly blunted in the CFS subjects compared with controls.

*

Dinan TG, Majeed T, Lavelle E, Scott LV, Berti C, Behan P. Blunted serotonin-mediated activation of the hypothalamic-pituitary-adrenal axis in chronic fatigue syndrome. *Psychoneuroendocrinology.* 1997 May;22(4):261-7. PMID: 9226729

Release of ACTH (but not cortisol) in response to ipsapirone challenge was significantly blunted in patients with CFS. The authors conclude that serotonergic activation of the hypothalamic-pituitary-adrenal axis is defective in CFS.

*

Cannon JG, Angel JB, Abad LW, Vannier E, Mileno MD, Fagioli L, Wolff SM, Komaroff AL. Interleukin-1 beta, interleukin-1 receptor antagonist, and soluble interleukin-1 receptor type II secretion in chronic fatigue syndrome. *J Clin Immunol.* 1997 May;17(3):253-61. PMID: 9168406

IL-1Ra secretion for CFS patients was twofold higher than controls during the follicular phase, but luteal-phase levels were similar between groups. In both phases of the menstrual cycle, IL-1sRII release was significantly higher for CFS patients compared to controls. These results suggest that an abnormality exists in IL-1 beta secretion in CFS patients that may be related to altered sensitivity to estradiol and progesterone. The increased release of IL-1Ra and sIL-1RII by cells from CFS patients is consistent with the hypothesis that CFS is associated with chronic, low-level activation of the immune system.

*

Allain TJ, Bearn JA, Coskeran P, Jones J, Checkley A, Butler J, Wessely S, Miell JP. Changes in growth hormone, insulin, insulinlike growth factors (IGFs), and IGF-binding protein-1 in chronic fatigue syndrome.

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Biol Psychiatry. 1997 Mar 1;41(5):567-73. PMID: 9046989

In CFS patients, the authors found attenuated basal levels of IGF-I and IGF-II; reduced GH response to hypoglycemia; higher insulin levels; and lower IGFBP-1 levels.

*

Sharpe M, Clements A, Hawton K, Young AH, Sargent P, Cowen PJ. Increased prolactin response to buspirone in chronic fatigue syndrome. *J Affect Disord.* 1996 Nov 4;41(1):71-6. PMID: 8938208

Patients with CFS had significantly higher plasma prolactin concentrations and experienced more nausea in response to buspirone than did controls.

*

Bearn J, Allain T, Coskeran P, Munro N, Butler J, McGregor A, Wessely S. Neuroendocrine responses to d-fenfluramine and insulin-induced hypoglycemia in chronic fatigue syndrome. *Biol Psychiatry.* 1995 Feb 15;37(4):245-52. PMID: 7711161

In a group of CFS patients, the researchers found attenuated prolactin responses to hypoglycemia, a greater ACTH response and higher peak ACTH concentrations.

Jefferies WM. Mild adrenocortical deficiency, chronic allergies, autoimmune disorders and the chronic fatigue syndrome: a continuation of the cortisone story. *Med Hypotheses.* 1994 Mar;42(3):183-9. PMID: 8057974

The author hypothesizes that CFS may be related to mild adrenocorticoid deficiency.

*

Bakheit AM, Behan PO, Watson WS, Morton JJ. Abnormal arginine-vasopressin secretion and water metabolism in patients with postviral fatigue syndrome. *Acta Neurol Scand.* 1993 Mar;87(3):234-8. PMID: 8475696

Patients with post viral fatigue syndrome had significantly low baseline arginine- vasopressin levels and evidence of increased total body water content, suggesting hypothalamic dysfunction.

*

Demitrack MA, Dale JK, Straus SE, Laue L, Listwak SJ, Kruesi MJ, Chrousos GP, Gold PW. Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome. *J Clin Endocrinol Metab.* 1991 Dec;73(6):1224-34. PMID: 1659582

CFS patients demonstrated significantly reduced basal evening glucocorticoid levels and low 24-h urinary free cortisol excretion, but elevated basal evening ACTH concentrations. There was increased adrenocortical sensitivity to ACTH, but a reduced maximal response. Patients showed attenuated net integrated ACTH responses to oCRH.

Appendix of Comments

Nervous System

Martínez-Martínez LA1, Mora T, Vargas A, Fuentes-Iniestra M, Martínez-Lavín M. Sympathetic nervous system dysfunction in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis: a review of case-control studies. *J Clin Rheumatol*. 2014 Apr;20(3):146-50. PMID: 24662556

A review of 186 articles suggests that sympathetic nervous system predominance is common in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis.

Brain Abnormalities

Nakatomi Y, Mizuno K, Ishii A, Wada Y, Tanaka M, Tazawa S, Onoe K, Fukuda S, Kawabe J, Takahashi K, Kataoka Y, Shiomi S, Yamaguti K, Inaba M, Kuratsune H, Watanabe Y. Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An 11C-(R)-PK11195 PET Study. *J Nucl Med*. 2014 Mar 24. PMID: 24665088

Testing using 11C-(R)-PK11195 and PET suggested that neuroinflammation is present in widespread brain areas in CFS patients and was associated with the severity of neuropsychologic symptoms.

*

Ishii A, Tanaka M, Iwamae M, Kim C, Yamano E, Watanabe Y. Fatigue sensation induced by the sounds associated with mental fatigue and its related neural activities: revealed by magnetoencephalography. *Behav Brain Funct*. 2013 Jun 13;9:24. PMID: 23764106

The researchers demonstrated that metronome sounds can cause mental fatigue sensation as a result of repeated pairings of the sounds with mental fatigue and that the insular cortex is involved in the neural substrates of this phenomenon.

*

He J, Hollingsworth KG, Newton JL, Blamire AM. Cerebral vascular control is associated with skeletal muscle pH in chronic fatigue syndrome patients both at rest and during dynamic stimulation. *Neuroimage Clin*. 2013 Jan 5;2:168-73. PMID: 24179772

Cerebral vascular control is closely related to skeletal muscle pH both at rest and after dynamic stimulation in CFS.

*

Puri BK, Jakeman PM, Agour M, Gunatilake KD, Fernando KA, Gurusinghe AI, Treasaden IH, Waldman AD, Gishen P. Regional grey and white matter volumetric changes in myalgic encephalomyelitis (chronic fatigue syndrome): a voxel-based morphometry 3 T MRI study. *Br J Radiol*. 2012 Jul;85(1015):e270-3. PMID: 22128128

Significant voxels depicting reduced grey matter volume in the CFS group were noted in the occipital lobes (right and left occipital poles; left lateral occipital cortex, superior division; and left supracalcrine cortex), the right angular gyrus and the posterior division of the left parahippocampal gyrus. Significant

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voxels depicting reduced white matter volume in the CFS group were also noted in the left occipital lobe. These data support the hypothesis that significant neuroanatomical changes occur in CFS.

Stewart JM, Medow MS, Messer ZR, Baugham IL, Terilli C, Ocon AJ. Postural neurocognitive and neuronal activated cerebral blood flow deficits in young chronic fatigue syndrome patients with postural tachycardia syndrome. *Am J Physiol Heart Circ Physiol*. 2012 Mar 1;302(5):H1185-94. PMID: 22180650

Cerebral blood flow velocity activation, normally tightly linked to cognitive neuronal activity, is unrelated to cognitive performance in CFS subjects; the increased critical closing pressure and vasomotor tone may indicate an uncoupling of the neurovascular unit during orthostasis.

*

Yamamoto S, Ouchi Y, Nakatsuka D, Tahara T, Mizuno K, Tajima S, Onoe H, Yoshikawa E, Tsukada H, Iwase M, Yamaguti K, Kuratsune H, Watanabe Y. Reduction of [¹¹C](+)-MPB binding in brain of chronic fatigue syndrome with serum autoantibody against muscarinic cholinergic receptor. *PLoS One*. 2012;7(12):e51515. PMID: 23240035

The study results demonstrate that serum autoantibody against the muscarinic cholinergic receptor (mAChR) can affect the brain mAChR without altering acetylcholinesterase activity and cognitive functions in CFS patients.

*

Puri BK, Jakeman PM, Agour M, Gunatilake KD, Fernando KA, Gurusinghe AI, Treasaden IH, Waldman AD, Gishen P. Regional grey and white matter volumetric changes in myalgic encephalomyelitis (chronic fatigue syndrome): a voxel-based morphometry 3-T MRI study. *Br J Radiol*. 2011 Nov 29. PMID: 22128128

Data from high-resolution structural 3-T cerebral MRI scanning support the hypothesis that significant neuroanatomical changes occur in CFS, and are consistent with the complaint of impaired memory that is common in this illness. They also suggest that subtle abnormalities in visual processing, and discrepancies between intended actions and consequent movements, may occur in CFS.

*

Biswal B, Kunwar P, Natelson BH. Cerebral blood flow is reduced in chronic fatigue syndrome as assessed by arterial spin labeling. *J Neurol Sci*. 2011 Feb 15;301(1-2):9- 11. PMID: 21167506

Most CFS patients have decreases in cerebral blood flow.

*

Perrin R, Embleton K, Pentreath VW, Jackson A. Longitudinal MRI shows no cerebral abnormality in chronic fatigue syndrome. *Br J Radiol*. 2010 May;83(989):419-23. PMID:20223910

No abnormal patterns in rate and extent of brain atrophy, ventricle volume, white matter lesions, cerebral blood flow or aqueductal CSF flow were detected in the CFS population.

*

Flor-Henry P, Lind JC, Koles ZJ. EEG source analysis of chronic fatigue syndrome. *Psychiatry Res*. 2010

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Feb 28;181(2):155-64. PMID: 20006474

During active cognitive conditions, a CFS group showed significantly greater source- current activity than the controls in the left frontal-temporal-parietal regions of the cortex.

*

Chen R, Liang FX, Moriya J, Yamakawa J, Sumino H, Kanda T, Takahashi T. Chronic fatigue syndrome and the central nervous system. *J Int Med Res.* 2008 Sep- Oct;36(5):867-74. PMID: 18831878

Neuroimaging evidence supports the hypothesis that chronic fatigue syndrome patients have structural or functional abnormalities within the brain.

*

Sherlin L, Budzynski T, Kogan Budzynski H, Congedo M, Fischer ME, Buchwald D. Low- resolution electromagnetic brain tomography (LORETA) of monozygotic twins discordant for chronic fatigue syndrome. *Neuroimage.* 2007 Feb 15;34(4):1438-42. PMID: 17169580

Neurophysiological activity in specific areas of the brain may differentiate individuals with CFS from those in good health. The study corroborates that slowing of the deeper structures of the limbic system is associated with affect. It also supports the neurobiological model that the right forebrain is associated with sympathetic activity and the left forebrain with the effective management of energy.

*

Sakudo A, Kuratsune H, Hakariya Y, Kobayashi T, Ikuta K. Spectroscopic diagnosis of chronic fatigue syndrome by multivariate analysis of visible and near-infrared spectra. *Nihon Rinsho.* 2007 Jun;65(6):1051-6. PMID: 17561696

*

Yoshiuchi K, Farkas J, Natelson BH. Patients with chronic fatigue syndrome have reduced absolute cortical blood flow. *Clin Physiol Funct Imaging.* 2006 Mar;26(2):83-6. PMID: 16494597

These data indicate that patients with CFS have reduced absolute cortical blood flow in rather broad areas when compared with data from healthy controls and that those devoid of psychopathology had the most reductions in cortical flow.

*

de Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, Toni I. Gray matter volume reduction in the chronic fatigue syndrome. *Neuroimage.* 2005 Jul 1;26(3):777-81. PMID: 15955487

There were significant reductions in global gray matter volume in CFS patients, and the decline in gray matter volume was linked to the reduction in physical activity.

*

Okada T, Tanaka M, Kuratsune H, Watanabe Y, Sadato N. Mechanisms underlying fatigue: a voxel-based morphometric study of chronic fatigue syndrome. *BMC Neurol.* 2004 Oct 4;4(1):14. PMID: 15461817

Patients with CFS had reduced gray-matter volume in the bilateral prefrontal cortex. Within these

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areas, the volume reduction in the right prefrontal cortex paralleled the severity of the fatigue of the subjects.

*

Schmaling KB, Lewis DH, Fiedelak JI, Mahurin R, Buchwald DS. Single-photon emission computerized tomography and neurocognitive function in patients with chronic fatigue syndrome. *Psychosom Med.* 2003 Jan-Feb;65(1):129-36. PMID: 12554824

No group differences were found for performance on single-photon emission computerized tomography scans despite CFS subjects' perceptions of exerting more mental effort to perform the task than healthy subjects. Inspection of the aggregate scans by group and task suggested a pattern of diffuse regional cerebral blood flow among subjects with CFS in comparison with the more focal pattern of regional cerebral blood flow seen among healthy subjects. Although CFS subjects showed less perfusion in the anterior cingulate region, the change in CFS subjects' activation of the left anterior cingulate region during the PASAT was greater than that observed for healthy subjects.

*

Chaudhuri A, Condon BR, Gow JW, Brennan D, Hadley DM. Proton magnetic resonance spectroscopy of basal ganglia in chronic fatigue syndrome. *Neuroreport.* 2003 Feb 10;14(2):225-8. PMID: 12598734

CFS has a dysfunction in the basal ganglia function, with an increase in the spectra from choline-containing compounds. This may be an indicator of higher cell membrane turnover due to gliosis or altered intramembrane signalling.

*

Puri BK, Counsell SJ, Zaman R, Main J, Collins AG, Hajnal JV, Davey NJ. Relative increase in choline in the occipital cortex in chronic fatigue syndrome. *Acta Psychiatr Scand.* 2002 Sep;106(3):224-6. PMID: 12197861

The mean ratio of choline to creatine in the occipital cortex in CFS was significantly higher than in the controls; thus, there may be an abnormality of phospholipid metabolism in the brain in CFS.

*

Brooks JC, Roberts N, Whitehouse G, Majeed T. Proton magnetic resonance spectroscopy and morphometry of the hippocampus in chronic fatigue syndrome. *Br J Radiol.* 2000 Nov;73(875):1206-8. PMID: 11144799

Proton magnetic resonance spectroscopy showed a significantly reduced concentration of N-acetylaspartate in the right hippocampus of CFS patients ($p = 0.005$).

*

MacHale SM, Lawrie SM, Cavanagh JT, Glabus MF, Murray CL, Goodwin GM, Ebmeier KP. Cerebral perfusion in chronic fatigue syndrome and depression. *Br J Psychiatry.* 2000 Jun;176:550-6. PMID: 10974961

Both CFS and depressive patients had increased perfusion in the right thalamus, pallidum and putamen. CFS patients also had increased perfusion in the left thalamus. Depressed patients differed from those with CFS in having relatively less perfusion of the left prefrontal cortex.

*

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Tomoda A, Miike T, Yamada E, Honda H, Moroi T, Ogawa M, Ohtani Y, Morishita S. Chronic fatigue syndrome in childhood. *Brain Dev.* 2000 Jan;22(1):60-4. PMID: 10761837

MR spectroscopy (MRS) study revealed remarkable elevation of the choline/creatine ratio in the three children with CFS. The authors suggest that the various clinical symptoms in CFS patients may be closely related to an abnormal brain function.

*

Lange G, DeLuca J, Maldjian JA, Lee H, Tiersky LA, Natelson BH. Brain MRI abnormalities exist in a subset of patients with chronic fatigue syndrome. *J Neurol Sci.* 1999 Dec 1;171(1):3-7. PMID: 10567042

On an MRI, cerebral changes in the CFS-No Psych group consisted mostly of small, punctate, subcortical white matter hyperintensities, found predominantly in the frontal lobes. This frontal lobe pathology could explain the more severe cognitive impairment previously reported in this subset of CFS patients.

*

Abu-Judeh HH, Levine S, Kumar M, el-Zeftawy H, Naddaf S, Lou JQ, Abdel-Dayem HM. Comparison of SPET brain perfusion and 18F-FDG brain metabolism in patients with chronic fatigue syndrome. *Nucl Med Commun.* 1998 Nov;19(11):1065-71. PMID: 9861623

In CFS, there is discordance between SPET brain perfusion and 18F-FDG brain uptake.

*

Tirelli U, Chierichetti F, Tavio M, Simonelli C, Bianchin G, Zanco P, Ferlin G. Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data. *Am J Med.* 1998 Sep 28;105(3A):54S-58S. PMID: 9790483

Positron emission tomography PET images of CFS patients showed a significant hypometabolism in the brainstem (having potential as a biomarker) and right mediofrontal cortex.

*

Lane RJ, Barrett MC, Taylor DJ, Kemp GJ, Lodi R. Heterogeneity in chronic fatigue syndrome: evidence from magnetic resonance spectroscopy of muscle. *Neuromuscul Disord.* 1998 May;8(3-4):204-9. PMID: 9631403

Some patients with chronic fatigue syndrome show an abnormal increase in plasma lactate following a short period of moderate exercise, in the sub-anaerobic threshold exercise test (SATET), and this cannot be explained satisfactorily by the effects of deconditioning.

*

Costa DC, Tannock C, Brostoff J. Brainstem perfusion is impaired in chronic fatigue syndrome. *QJM.* 1995 Nov;88(11):767-73. PMID: 8542261

Patients with ME/CFS were found to have a generalized reduction of brain perfusion, with a particular pattern of hypoperfusion of the brainstem.

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Schwartz RB, Garada BM, Komaroff AL, Tice HM, Gleit M, Jolesz FA, Holman BL. Detection of intracranial abnormalities in patients with chronic fatigue syndrome: comparison of MR imaging and SPECT. *AJR Am J Roentgenol.* 1994 Apr;162(4):935-41. PMID: 8141020

SPECT abnormalities occur more frequently and in greater numbers than MR abnormalities do in patients with CFS.

*

Natelson BH, Cohen JM, Brassloff I, Lee HJ. A controlled study of brain magnetic resonance imaging in patients with the chronic fatigue syndrome. *J Neurol Sci.* 1993 Dec 15;120(2):213-7. PMID: 8138812

Abnormalities in brain scans indicates that some CFS patients have some organic problem manifesting itself on neuroimaging.

*

Buchwald D, Cheney PR, Peterson DL, Henry B, Wormsley SB, Geiger A, Ablashi DV, Salahuddin SZ, Saxinger C, Biddle R, et al. A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpesvirus type 6 infection. *Ann Intern Med.* 1992 Jan 15;116(2):103-13. PMID: 1309285

CFS patients had a higher mean CD4/CD8 T-cell ratio than matched healthy controls. Magnetic resonance scans of the brain showed punctate, subcortical areas of high signal intensity consistent with edema or demyelination in 78% of patients.

*

Shimizu T. Neuro-psychiatric aspects of chronic fatigue syndrome. *Nihon Rinsho.* 1992 Nov;50(11):2630-4. PMID: 1287239

Study of brain blood flow or metabolism by PET or SPECT is a possible tool for establishment of the CFS identity.

*

Ichise M, Salit IE, Abbey SE, Chung DG, Gray B, Kirsh JC, Freedman M. Assessment of regional cerebral perfusion by 99Tcm-HMPAO SPECT in chronic fatigue syndrome. *Nucl Med Commun.* 1992 Oct;13(10):767-72. PMID: 1491843

CFS patients showed abnormally low cortical/cerebellar rCBF ratios, throughout multiple brain regions. 80% showed at least one or more rCBF ratios significantly less than normal values. The major cerebral regions involved were frontal (63%), temporal (35%), parietal (53%) and occipital lobes (38%). The rCBF ratios of basal ganglia were also reduced.

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Cognitive Impairment

Cockshell SJ, Mathias JL. Cognitive deficits in chronic fatigue syndrome and their relationship to psychological status, symptomatology, and everyday functioning. *Neuropsychology*. 2013 Mar;27(2):230-42. PMID: 23527651

Compared to controls, a group of CFS patients showed impaired information processing speed (reaction time) but comparable performance on tests of attention, memory, motor functioning, verbal ability, and visuospatial ability. Moreover, information processing speed was not related to psychiatric status, depression, anxiety, the number or severity of CFS symptoms, fatigue, sleep quality, or everyday functioning.

*

Togo F, Lange G, Natelson BH, Quigley KS. Attention network test: Assessment of cognitive function in chronic fatigue syndrome. *J Neuropsychol*. 2013 Sep 24. PMID: 24112872

Comparison of data from two groups of CFS patients (those with and without comorbid major depressive disorder) to controls consistently showed that error rates did not differ among groups across conditions, but speed of information processing did. Processing time was prolonged in both CFS groups and most significantly affected in response to the most complex task conditions. For simpler tasks, processing time was only prolonged in CFS participants with depression.

*

Hutchinson CV, Badham SP. Patterns of Abnormal Visual Attention in Myalgic Encephalomyelitis. *Optom Vis Sci*. 2013 May 17. PMID: 23689679

In a study of visual attention difficulties, CFS patients exhibited marginally worse performance compared with controls on the divided attention subtest and significantly worse performance on the selective attention subtest. In the spatial cueing task, they were slower than controls to respond to the presence of the target, particularly when cues were invalid. They were also impaired, relative to controls, on visual search tasks.

*

Mizuno K, Watanabe Y. Neurocognitive impairment in childhood chronic fatigue syndrome. *Front Physiol*. 2013 Apr 19;4:87. PMID: 23626579

Neurocognitive impairment (including reduced attention control in switching and divided-attention tasks) is a feature of childhood chronic fatigue syndrome.

*

Beaumont A, Burton AR, Lemon J, Bennett BK, Lloyd A, Vollmer-Conna U. Reduced cardiac vagal modulation impacts on cognitive performance in chronic fatigue syndrome. *PLoS One*. 2012;7(11):e49518. PMID: 23166694

In a cognitive task study, patients with CFS showed no deficits in performance accuracy, but were significantly slower than healthy controls. CFS was further characterized by low and unresponsive heart rate variability; greater heart rate (HR) reactivity and prolonged HR-recovery after cognitive challenge.

*

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Cockshell SJ, Mathias JL. Test effort in persons with Chronic Fatigue Syndrome when assessed using the Validity Indicator Profile. *J Clin Exp Neuropsychol*. 2012;34(7):679- 87. PMID: 22440059

This study's findings suggest that poor effort is unlikely to contribute to cognitive test performance of persons with CFS.

*

Constant EL, Adam S, Gillain B, Lambert M, Masquelier E, Seron X. Cognitive deficits in patients with chronic fatigue syndrome compared to those with major depressive disorder and healthy controls. *Clin Neurol Neurosurg*. 2011 Jan 19. PMID: 21255911

CFS patients have objective impairments in attention and memory, but with good motivation and without exaggerated suggestibility.

*

Ocon AJ. Caught in the thickness of brain fog: exploring the cognitive symptoms of Chronic Fatigue Syndrome. *Front Physiol*. 2013;4:63. PMID: 23576989

The cognitive symptoms of CFS may be due to altered cerebral blood flow activation and regulation that are exacerbated by a stressor, such as orthostasis or a difficult mental task, resulting in the decreased ability to readily process information.

*

Kawatani J, Mizuno K, Shiraishi S, Takao M, Joudoi T, Fukuda S, Watanabe Y, Tomoda A. Cognitive dysfunction and mental fatigue in childhood chronic fatigue syndrome - A 6- month follow-up study. *Brain Dev*. 2011 Apr 27. PMID: 21530119

Higher-order level cognitive dysfunction affects childhood CFS pathogenesis. Alternative attention performance evaluated by the mATMT may be used to monitor improvement in patients with CCFS. Combined treatment with CBT and medication may be effective to improve poor attention characteristics associated with CCFS.

*

Kadota Y, Cooper G, Burton AR, Lemon J, Schall U, Lloyd A, Vollmer-Conna U. Autonomic hyper-vigilance in post-infective fatigue syndrome. *Biol Psychol*. 2010 Sep;85(1):97-103. PMID: 20678991

Post-infective fatigue syndrome (PIFS) is associated with a disturbance in bidirectional autonomic signalling resulting in heightened perception of symptoms and sensations from the body in conjunction with autonomic hyper-reactivity to perceived challenges.

*

Thomas M, Smith A. An investigation into the cognitive deficits associated with chronic fatigue syndrome. *Open Neurol J*. 2009 Feb 27;3:13-23. PMID: 19452031

CFS patients demonstrate specific cognitive impairments.

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Dickson A, Toft A, O'Carroll RE. Neuropsychological functioning, illness perception, mood and quality of life in chronic fatigue syndrome, autoimmune thyroid disease and healthy participants. *Psychol Med.* 2009 Sep;39(9):1567-76. PMID: 19144216

The results of this study suggest that the primary cognitive impairment in CFS is attention and that this is not secondary to affective status. The lower treatment control perceptions and greater illness concerns that CFS patients report may be causally related to their affective status.

*

Schrijvers D, Van Den Eede F, Maas Y, Cosyns P, Hulstijn W, Sabbe BG. Psychomotor functioning in chronic fatigue syndrome and major depressive disorder: a comparative study. *J Affect Disord.* 2009 May;115(1-2):46-53. PMID: 18817977

Patients with CFS or depression demonstrated overall fine motor slowing and similar cognitive impairments.

*

Haig-Ferguson A, Tucker P, Eaton N, Hunt L, Crawley E. Memory and attention problems in children with chronic fatigue syndrome or myalgic encephalopathy. *Arch Dis Child.* 2009 Oct;94(10):757-62. PMID: 19001478

Children with CFS/ME appear to experience problems with attention, which may have adverse implications for verbal memory.

*

Majer M, Welberg LA, Capuron L, Miller AH, Pagnoni G, Reeves WC. Neuropsychological performance in persons with chronic fatigue syndrome: results from a population-based study. *Psychosom Med.* 2008 Sep;70(7):829-36. PMID: 18606722

CFS patients have alterations in motor speed and working memory independent of comorbid psychiatric disease and medication usage.

*

Claypoole KH, Noonan C, Mahurin RK, Goldberg J, Erickson T, Buchwald D. A twin study of cognitive function in chronic fatigue syndrome: the effects of sudden illness onset. *Neuropsychology.* 2007 Jul;21(4):507-13. PMID: 17605583

In a study of CFS patients and healthy identical twins, patients exhibited decreases in motor functions, speed of information processing, verbal memory, and executive functioning.

*

Glass JM. Cognitive dysfunction in fibromyalgia and chronic fatigue syndrome: new trends and future directions. *Curr Rheumatol Rep.* 2006 Dec;8(6):425-9. PMID: 17092441

CFS patients often have memory and cognitive complaints. Neuroimaging studies demonstrate cerebral abnormalities and a pattern of increased neural recruitment during cognitive tasks.

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Capuron L, Welberg L, Heim C, Wagner D, Solomon L, Papanicolaou DA, Craddock RC, Miller AH, Reeves WC. Cognitive dysfunction relates to subjective report of mental fatigue

in patients with chronic fatigue syndrome. *Neuropsychopharmacology*. 2006 Aug;31(8):1777-84. PMID: 16395303

This study shows strong concordance between subjective complaints of mental fatigue and objective measurement of cognitive impairment in CFS patients and suggests that mental fatigue is an important component of CFS-related cognitive dysfunction.

*

Tanaka M, Sadato N, Okada T, Mizuno K, Sasabe T, Tanabe HC, Saito DN, Onoe H, Kuratsune H, Watanabe Y. Reduced responsiveness is an essential feature of chronic fatigue syndrome: a fMRI study. *BMC Neurol*. 2006 Feb 22;6:9. PMID: 16504053

CFS may be characterised by attenuation of the responsiveness to stimuli not directly related to the fatigue-inducing task.

*

Caseras X, Mataix-Cols D, Giampietro V, Rimes KA, Brammer M, Zelaya F, Chalder T, Godfrey EL. Probing the working memory system in chronic fatigue syndrome: a functional magnetic resonance imaging study using the n-back task. *Psychosom Med*. 2006 Nov-Dec;68(6):947-55. PMID: 17079703

Patients with CFS show both quantitative and qualitative differences in activation of the working memory network compared with healthy control subjects.*

*

Cook DB, Nagelkirk PR, Peckerman A, Poluri A, Mores J, Natelson BH. Exercise and cognitive performance in chronic fatigue syndrome. *Med Sci Sports Exerc*. 2005 Sep;37(9):1460-7. PMID: 16177595

CFS patients without comorbid FM exhibit subtle cognitive deficits in terms of speed, consistency, and efficiency that are not improved or exacerbated by light exercise.

*

Schillings ML, Kalkman JS, van der Werf SP, van Engelen BG, Bleijenberg G, Zwarts MJ. Diminished central activation during maximal voluntary contraction in chronic fatigue syndrome. *Clin Neurophysiol*. 2004 Nov;115(11):2518-24. PMID: 15465441

Central activation is diminished in CFS patients. Possible causes include changed perception, impaired concentration, reduced effort and physiologically defined changes, e.g. in the corticospinal excitability or the concentration of neurotransmitters. As a consequence, demands on the muscle are lower, resulting in less peripheral fatigue.

*

Deluca J, Christodoulou C, Diamond BJ, Rosenstein ED, Kramer N, Natelson BH. Working memory deficits in chronic fatigue syndrome: differentiating between speed and accuracy of information

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processing. *J Int Neuropsychol Soc.* 2004 Jan;10(1):101-9. PMID: 14751012

Compared to healthy controls (HC) and a group of participants with rheumatoid arthritis (RA), the CFS-noPsych group displayed significantly reduced performance on tests of information processing speed, but not on tests of working memory.

*

Davey NJ, Puri BK, Catley M, Main J, Nowicky AV, Zaman R. Deficit in motor performance correlates with changed corticospinal excitability in patients with chronic fatigue syndrome. *Int J Clin Pract.* 2003 May;57(4):262-4. PMID: 12800454

This study provides evidence that changing motor deficits in CFS have a neurophysiological basis. The slowness of simple reaction times supports the notion of a deficit in motor preparatory areas of the brain.

*

Michiels V, Cluydts R. Neuropsychological functioning in chronic fatigue syndrome: a review. *Acta Psychiatr Scand.* 2001 Feb;103(2):84-93. PMID: 11167310

The current research shows that slowed processing speed, impaired working memory and poor learning of information are the most prominent features of cognitive dysfunctioning in patients with CFS.

*

Friedberg F, Dechene L, McKenzie MJ 2nd, Fontanetta R. Symptom patterns in long- duration chronic fatigue syndrome. *J Psychosom Res.* 2000 Jan;48(1):59-68. PMID: 10750631

People with long-duration CFS reported a large number of specific cognitive difficulties that were greater in severity than those reported by participants with short-duration CFS. The pattern of comorbid disorders in the CFS groups was consistent with hypersensitivity and viral reactivation hypotheses.

*

Michiels V, Cluydts R, Fischler B. Attention and verbal learning in patients with chronic fatigue syndrome. *J Int Neuropsychol Soc.* 1998 Sep;4(5):456-66. PMID: 9745235

CFS patients were poorer than controls on recall of verbal information.

*

Michiels V, Cluydts R, Fischler B, Hoffmann G, Le Bon O, De Meirleir K. Cognitive functioning in patients with chronic fatigue syndrome. *J Clin Exp Neuropsychol.* 1996 Oct;18(5):666-77. PMID: 8941852

The learning rate of verbal and visual material for patients with CFS was slower, and delayed recall of verbal and visual information was impaired, compared to normals. There was a high variability in cognitive impairment within the CFS group. The neuropsychological variables of psychomotor performance and verbal memory were found to discriminate best between patients and controls.

*

Marcel B, Komaroff AL, Fagioli LR, Kornish RJ 2nd, Albert MS. Cognitive deficits in patients with chronic fatigue syndrome. *Biol Psychiatry.* 1996 Sep 15;40(6):535-41. PMID: 8879474

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A subset of CFS patients may experience significant impairments in learning and memory.

*

Johnson SK, DeLuca J, Diamond BJ, Natelson BH. Selective impairment of auditory processing in chronic fatigue syndrome: a comparison with multiple sclerosis and healthy controls. *Percept Mot Skills*. 1996 Aug;83(1):51-62. PMID: 8873173

CFS patients are more impaired on auditory than on visual processing tasks.

*

Joyce E, Blumenthal S, Wessely S. Memory, attention, and executive function in chronic fatigue syndrome. *J Neurol Neurosurg Psychiatry*. 1996 May;60(5):495-503. PMID: 8778252

Patients with chronic fatigue syndrome have reduced attentional capacity resulting in impaired performance on effortful tasks requiring planned or self ordered generation of responses from memory.

*

Johnson SK, DeLuca J, Fiedler N, Natelson BH. Cognitive functioning of patients with chronic fatigue syndrome. *Clin Infect Dis*. 1994 Jan;18 Suppl 1:S84-5. PMID: 8148459

Impaired information processing, rather than primary memory dysfunction, may be at the root of the cognitive problems that afflict so many patients with CFS.

*

Sandman CA, Barron JL, Nackoul K, Goldstein J, Fidler F. Memory deficits associated with chronic fatigue immune dysfunction syndrome. *Biol Psychiatry*. 1993 Apr 15-May 1;33(8-9):618-23. PMID: 8329493

A study of CFS patients revealed significant memory deficits consistent with temporal- limbic dysfunction.

*

DeLuca J, Johnson SK, Natelson BH. Information processing efficiency in chronic fatigue syndrome and multiple sclerosis. *Arch Neurol*. 1993 Mar;50(3):301-4. PMID: 8442710

Subjects with CFS showed significant impairment on a test of complex concentration.

*

Scheffers MK, Johnson R Jr, Grafman J, Dale JK, Straus SE. Attention and short-term memory in chronic fatigue syndrome patients: an event-related potential analysis. *Neurology*. 1992 Sep;42(9):1667-75. PMID: 1513453

Cognitive impairment in CFS involves response-related processes.

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Gait Abnormalities

Paul L, Rafferty D, Wood L, Maclaren W. Gait characteristics of subjects with chronic fatigue syndrome and controls at self-selected and matched velocities. *J Neuroeng Rehabil.* 2008 May 27;5:16. PMID: 18505580

Gait velocity or pattern can be used to monitor patients' progress in CFS.

*

Paul LM, Wood L, Maclaren W. The effect of exercise on gait and balance in patients with chronic fatigue syndrome. *Gait Posture.* 2001 Jul;14(1):19-27. PMID: 11378421

CFS patients were different in gait parameter than normal people. Heart rate responses demonstrated that both groups were exercising at similar loads, although this was perceived to be higher by the CFS group.

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Saggini R, Pizzigallo E, Vecchiet J, Macellari V, Giacomozzi C. Alteration of spatial-temporal parameters of gait in Chronic Fatigue Syndrome patients. *J Neurol Sci.* 1998 Jan 21;154(1):18-25. PMID: 9543318

The gait of CFS patients revealed significant abnormalities in the symmetry indices of the bilateral parameters and in the linear relationships among parameters, and between these parameters and the physical characteristics of the patients. The abnormalities were present as from the beginning of the gait, which indicates that they are unlikely to be caused by the rapid increasing fatigue. This strengthens the hypothesis of a direct involvement of the central nervous system (CNS) in the onset of the disease.

*

Boda WL, Natelson BH, Sisto SA, Tapp WN. Gait abnormalities in chronic fatigue syndrome. *J Neurol Sci.* 1995 Aug;131(2):156-61. PMID: 7595641

The researchers evaluated their clinical impression that patients with CFS did not walk normally, finding that they did indeed have objective gait abnormalities.

Sleep Abnormalities

Gotts ZM, Deary V, Newton J, Van der Dussen D, De Roy P, Ellis JG. Are there sleep-specific phenotypes in patients with chronic fatigue syndrome? A cross-sectional polysomnography analysis. *BMJ Open.* 2013 Jun 20;3(6). PMID: 23794547

Of 343 patients with CFS, 30.3% were identified with a Primary Sleep Disorder explaining their diagnosis. Of the remaining patients, 89.1% met quantitative criteria for at least one objective sleep problem.

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Togo F, Natelson BH. Heart rate variability during sleep and subsequent sleepiness in patients with chronic fatigue syndrome. *Auton Neurosci*. 2013 Jun;176(1-2):85-90. PMID: 23499514

Results of this study suggest that beat-to-beat RR interval dynamics or autonomic nervous system activity during non-REM sleep might be associated with disrupted sleep in patients with CFS.

Mariman AN, Vogelaers DP, Tobback E, Delesie LM, Hanouille IP, Pevernagie DA. Sleep in the chronic fatigue syndrome. *Sleep Med Rev*. 2013 Jun;17(3):193-9. PMID:23046847

There is currently insufficient evidence to indicate that treatment of primary sleep disorders sufficiently improves the fatigue associated with CFS. Therefore, primary sleep disorders may be a comorbid rather than an exclusionary condition with respect to CFS.

*

Le Bon O, Neu D, Berquin Y, Lanquart JP, Hoffmann R, Mairesse O, Armitage R. Ultra- slow delta power in chronic fatigue syndrome. *Psychiatry Res*. 2012 Dec 30;200(2-3):742- 7. PMID: 22771174

CFS is associated with lower ultra-slow (0.5-0.8Hz) delta power, underscoring the importance of looking beyond conventional EEG frequency bands.

*

Mariman A, Vogelaers D, Hanouille I, Delesie L, Pevernagie D. Subjective sleep quality and daytime sleepiness in a large sample of patients with chronic fatigue syndrome (CFS). *Acta Clin Belg*. 2012 Jan-Feb;67(1):19-24. PMID: 22480034

A distinct subgroup of CFS patients with clinical features of insomnia and specific sleep problems was identified.

*

Jackson ML, Bruck D. Sleep abnormalities in chronic fatigue syndrome/myalgic encephalomyelitis: a review. *J Clin Sleep Med*. 2012 Dec 15;8(6):719-28. PMID:23243408

This review provides a comprehensive overview of the literature examining sleep in CFS/ME and the issues surrounding the current research findings.

*

Mariman A, Vogelaers D, Hanouille I, Delesie L, Tobback E, Pevernagie D. Validation of the three-factor model of the PSQI in a large sample of chronic fatigue syndrome (CFS) patients. *J Psychosom Res*. 2012 Feb;72(2):111-3. PMID: 22281451

Sleep disturbances in CFS were evaluated according to the Pittsburgh Sleep Quality Index (PSQI) scale.

*

Wu HS, Davis JE, Natavio T. Fatigue and disrupted sleep-wake patterns in patients with cancer: a shared mechanism. *Clin J Oncol Nurs*. 2012 Apr;16(2):E56-68. PMID: 22459538

The strong and potentially reciprocal relationship between cancer-related fatigue (CRF) and disrupted sleep-wake patterns suggests a possible shared physiologic pathway.

Appendix of Comments

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Kishi A, Natelson BH, Togo F, Struzik ZR, Rapoport DM, Yamamoto Y. Sleep-Stage Dynamics in Patients with Chronic Fatigue Syndrome with or without Fibromyalgia. *Sleep*. 2011 Nov 1;34(11):1551-60. PMID: 22043126

The probability of transition from REM sleep to waking was significantly greater in subjects with CFS alone than in control subjects. Probabilities of (a) transitions from waking, REM sleep, and S1 to S2 and (b) those from SWS to waking and S1 were significantly greater in subjects with CFS+FM than in control subjects; in addition, rates of these transitions were also significantly increased in subjects with CFS+FM. These results suggest that CFS and FM may be different illnesses associated with different problems of sleep regulation.

*

Spitzer AR, Broadman M. Treatment of the narcoleptiform sleep disorder in chronic fatigue syndrome and fibromyalgia with sodium oxybate. *Pain Pract*. 2010 Jan- Feb;10(1):54-9. PMID: 20629967

Abnormal findings on sleep studies and associated human leukocyte antigen markers, and a clinical pattern suggestive of narcolepsy, are present in a high proportion of CFS and fibromyalgia patients. Sixty percent of patients treated with oxybate experienced significant relief of pain, while 75% experienced significant relief of fatigue. The authors postulate that the response to oxybate in CFS and FM suggests a disturbance of sleep similar to narcolepsy.

*

Kishi A, Natelson BH, Togo F, Struzik ZR, Rapoport DM, Yamamoto Y. Sleep stage transitions in chronic fatigue syndrome patients with or without fibromyalgia. *Conf Proc IEEE Eng Med Biol Soc*. 2010;2010:5391-4. PMID: 21096267

CFS includes specific sleep problems, including difficulties in transitioning from REM sleep to wakening.

Neu D, Kajosch H, Peigneux P, Verbanck P, Linkowski P, Le Bon O. Cognitive impairment in fatigue and sleepiness associated conditions. *Psychiatry Res*. 2010 Dec 31. PMID: 21196050

CFS patients have sleep disorders that prompt cognitive and behavioural motor performance.

*

Creti L, Libman E, Baltzan M, Rizzo D, Bailes S, Fichten CS. Impaired sleep in chronic fatigue syndrome: how is it best measured? *J Health Psychol*. 2010 May;15(4):596-607. PMID: 20460416

In CFS: (a) objectively measured nocturnal sleep time effectively approximated subjective experience although nocturnal wakefulness did not; (b) total sleep time and sleep efficiency differentiated individuals with and without insomnia complaints; (c) daytime sleepiness, fatigue, and non-refreshing sleep were not reflected by the objective sleep-related measures (polysomnography and actigraphy).

*

Togo F, Natelson BH, Cherniack NS, Klapholz M, Rapoport DM, Cook DB. Sleep is not disrupted by exercise in patients with chronic fatigue syndromes. *Med Sci Sports Exerc*. 2010 Jan;42(1):16-22. PMID: 20010134

Sleep is disturbed in CFS patients as a group, but exercise does not exacerbate this sleep disturbance.

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Decker MJ, Tabassum H, Lin JM, Reeves WC. Electroencephalographic correlates of Chronic Fatigue Syndrome. *Behav Brain Funct.* 2009 Oct 6;5:43. PMID: 19807920

In persons with CFS, delta power was diminished during slow wave sleep, but elevated during both stage 1 and REM. Alpha power was reduced during stage 2, slow wave, and REM sleep. Those with CFS also had significantly lower theta, sigma, and beta spectral power during stage 2, Slow Wave Sleep, and REM.

*

Libman E, Creti L, Baltzan M, Rizzo D, Fichten CS, Bailes S. Sleep apnea and psychological functioning in chronic fatigue syndrome. *J Health Psychol.* 2009 Nov;14(8):1251-67. PMID: 19858344

CFS participants with and without sleep apnea/hypopnea syndrome did not differ on various measures. The authors conclude that SAHS should not be an exclusion criterion for CFS.

*

Neu D, Cappeliez B, Hoffmann G, Verbanck P, Linkowski P, Le Bon O. High slow-wave sleep and low-light sleep: chronic fatigue syndrome is not likely to be a primary sleep disorder. *J Clin Neurophysiol.* 2009 Jun;26(3):207-12. PMID: 19424087

Sleep efficiency was lower in both CFS than controls. CFS patients showed a higher microarousal index than controls. Anxiety, but not depression symptoms were more intense in the CFS group. The distribution of nonrapid eye movement sleep in CFS differs sizeably from what can be observed in a primary sleep disorder.

*

Armitage R, Landis C, Hoffmann R, Lentz M, Watson N, Goldberg J, Buchwald D. Power spectral analysis of sleep EEG in twins discordant for chronic fatigue syndrome. *J Psychosom Res.* 2009 Jan;66(1):51-7. PMID: 19073294

No significant differences in spectral power in any frequency band in a sleep study were found between those with CFS and their nonfatigued cotwins.

*

Neu D, Hoffmann G, Moutrier R, Verbanck P, Linkowski P, Le Bon O. Are patients with chronic fatigue syndrome just 'tired' or also 'sleepy'? *J Sleep Res.* 2008 Dec;17(4):427-31. PMID: 19021860

The "fatigue" in CFS is not exactly the same as normal sleepiness.

*

Togo F, Natelson BH, Cherniack NS, FitzGibbons J, Garcon C, Rapoport DM. Sleep structure and sleepiness in chronic fatigue syndrome with or without coexisting fibromyalgia. *Arthritis Res Ther.* 2008;10(3):R56. PMID: 18474105

CFS patients had significant differences in polysomnographic findings from healthy controls and felt sleepier and more fatigued than controls after a night's sleep. This difference was due primarily to a decrease in the length of periods of uninterrupted sleep in the patients with more sleepiness in the morning than on the night before.

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Kishi A, Struzik ZR, Natelson BH, Togo F, Yamamoto Y. Dynamics of sleep stage transitions in healthy humans and patients with chronic fatigue syndrome. *Am J Physiol Regul Integr Comp Physiol*. 2008 Jun;294(6):R1980-7. PMID: 18417644

Specific sleep problems in CFS are examined.

*

Majer M, Jones JF, Unger ER, Youngblood LS, Decker MJ, Gurbaxani B, Heim C, Reeves WC. Perception versus polysomnographic assessment of sleep in CFS and non-fatigued control subjects: results from a population-based study. *BMC Neurol*. 2007 Dec 5;7:40. PMID: 18053240

People with CFS reported sleep problems significantly more often than control subjects. Yet, when measured these parameters and sleep architecture did not differ between the two subject groups.

*

Ohinata J, Suzuki N, Araki A, Takahashi S, Fujieda K, Tanaka H. Actigraphic assessment of sleep disorders in children with chronic fatigue syndrome. *Brain Dev*. 2008 May;30(5):329-33. PMID: 18031961

Compared to the control group, total sleep time was longer and physical activity was lower in CFS.

*

Neu D, Mairesse O, Hoffmann G, Dris A, Lambrecht LJ, Linkowski P, Verbanck P, Le Bon O. Sleep quality perception in the chronic fatigue syndrome: correlations with sleep efficiency, affective symptoms and intensity of fatigue. *Neuropsychobiology*. 2007;56(1):40-6. PMID: 17986836

CFS patients reported poor quality sleep, but objective sleep quality parameters, like the Sleep Efficiency Index (SEI) or the amount of slow-wave sleep did not differ significantly.

*

Tajima S, Kuratsune H, Yamaguti K, Takahashi A, Takashima S, Watanabe Y, Nishizawa Y. Estimation of fatigue state in patient with CFS using actigraph and R-R interval power spectrum analysis. *Nihon Rinsho*. 2007 Jun;65(6):1057-64. PMID: 17561697

Actigraphy analysis showed that mean awake activity was decreased and duration of sleep was prolonged in patients with CFS.

Kumano-go T, Adachi H, Sugita Y. Sleep disturbance in chronic fatigue syndrome. *Nihon Rinsho*. 2007 Jun;65(6):1017-22. PMID: 17561691

CFS patients display a variety of sleep disorders.

*

Armitage R, Landis C, Hoffmann R, Lentz M, Watson NF, Goldberg J, Buchwald D. The impact of a 4-hour sleep delay on slow wave activity in twins discordant for chronic fatigue syndrome. *Sleep*. 2007 May;30(5):657-62. PMID: 17552382

CFS is associated with a blunted slow wave analysis response to sleep challenge, suggesting that the

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basic sleep drive and homeostatic response are impaired.

*

Van Hoof E, De Becker P, Lapp C, Cluydts R, De Meirleir K. Defining the occurrence and influence of alpha-delta sleep in chronic fatigue syndrome. *Am J Med Sci.* 2007 Feb;333(2):78-84. PMID: 17301585

CFS patients experienced a prolonged sleep latency, showed a low sleep efficiency index, and had a low percentage of slow wave sleep.

*

Reeves WC, Heim C, Maloney EM, Youngblood LS, Unger ER, Decker MJ, Jones JF, Rye DB. Sleep characteristics of persons with chronic fatigue syndrome and non-fatigued controls: results from a population-based study. *BMC Neurol.* 2006 Nov 16;6:41. PMID: 17109739

Although disordered breathing during sleep may be associated with CFS, this study generally did not provide evidence that altered sleep architecture is a critical factor in CFS.

*

Guilleminault C, Poyares D, Rosa A, Kirisoglu C, Almeida T, Lopes MC. Chronic fatigue, unrefreshing sleep and nocturnal polysomnography. *Sleep Med.* 2006 Sep;7(6):513-20. PMID: 16934523

The complaints of chronic fatigue and unrefreshing sleep were associated with an abnormal cyclic alternating pattern rate, with increase in slow delta power spectrum, affirming the presence of an abnormal sleep progression and non-rapid eye movement sleep instability. These specific patterns were related to subtle, undiagnosed sleep- disordered breathing.

*

Unger ER, Nisenbaum R, Moldofsky H, Cesta A, Sammut C, Reyes M, Reeves WC. Sleep assessment in a population-based study of chronic fatigue syndrome. *BMC Neurol.* 2004 Apr 19;4:6. PMID: 15096280

Sleep issues were examined for a population of CFS patients in Wichita, Kansas. 81.4% of subjects had an abnormality in at least one SAQ sleep factor. Subjects with sleep factor abnormalities had significantly lower wellness scores but statistically unchanged fatigue severity scores compared to those without SAQ abnormality.

*

Hamilos DL, Nutter D, Gershtenson J, Ikle D, Hamilos SS, Redmond DP, Di Clementi JD, Schmaling KB, Jones JF. Circadian rhythm of core body temperature in subjects with chronic fatigue syndrome. *Clin Physiol.* 2001 Mar;21(2):184-95. PMID: 11318826

In ambulatory conditions, the circadian rhythm of CBT in CFS is nearly indistinguishable from that of normal control subjects although there was a tendency for greater variability in the rhythm. Hence, it is unlikely that the symptoms of CFS are because of disturbance in the circadian rhythm of CBT.

*

Stores G, Fry A, Crawford C. Sleep abnormalities demonstrated by home polysomnography in teenagers with chronic fatigue syndrome. *J Psychosom Res.* 1998 Jul;45(1 Spec No):85-91. PMID: 9720858

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Compared with controls, teenagers with CFS showed significantly higher levels of sleep disruption by both brief and longer awakenings.

*

Morriss RK, Wearden AJ, Battersby L. The relation of sleep difficulties to fatigue, mood and disability in chronic fatigue syndrome. *J Psychosom Res.* 1997 Jun;42(6):597-605. PMID: 9226607

CFS patients reported significantly more naps and waking by pain, a similar prevalence of difficulties in maintaining sleep, and significantly less difficulty getting off to sleep compared to depressed patients. Sleep continuity complaints preceded fatigue in only 20% of CFS patients, but there was a strong association between relapse and sleep disturbance. Disrupted sleep appears to complicate the course of CFS. Sleep complaints in CFS do not seem related to depression.

Bennett AL, Mayes DM, Fagioli LR, Guerriero R, Komaroff AL. Somatomedin C (insulin-like growth factor I) levels in patients with chronic fatigue syndrome. *J Psychiatr Res.* 1997 Jan-Feb;31(1):91-6. PMID: 9201651

In contrast to patients with fibromyalgia, in whom levels of somatomedin C have been found to be reduced, levels in patients with CFS were found to be elevated. Thus, despite the clinical similarities between these two conditions, they may be associated with different abnormalities of sleep and/or of the somatotrophic neuroendocrine axis.

*

Fischler B, Le Bon O, Hoffmann G, Cluydts R, Kaufman L, De Meirleir K. Sleep anomalies in the chronic fatigue syndrome. A comorbidity study. *Neuropsychobiology.* 1997;35(3):115-22. PMID: 9170115

CFS sufferers were different than controls on variables of sleep-onset latency and the number of stage shifts/hour.

*

Williams G, Pirmohamed J, Minors D, Waterhouse J, Buchan I, Arendt J, Edwards RH. Dissociation of body-temperature and melatonin secretion circadian rhythms in patients with chronic fatigue syndrome. *Clin Physiol.* 1996 Jul;16(4):327-37. PMID: 8842569

CFS patients showed no significant correlation between the timing of the temperature acrophase and the melatonin onset, whereas the normal significant correlation was observed in the controls. Dissociation of circadian rhythms could be due to the sleep deprivation and social disruption, and/or the reduction in physical activity which typically accompany CFS.

*

Schaefer KM. Sleep disturbances and fatigue in women with fibromyalgia and chronic fatigue syndrome. *J Obstet Gynecol Neonatal Nurs.* 1995 Mar-Apr;24(3):229-33. PMID: 7782955

Women with CFS encounter problems with quality as well as amount of sleep.

*

Manu P, Lane TJ, Matthews DA, Castriotta RJ, Watson RK, Abeles M. Alpha-delta sleep in patients with a chief complaint of chronic fatigue. *South Med J.* 1994 Apr;87(4):465-70. PMID: 8153772

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Alpha-delta sleep is not a marker of CFS, but may contribute to the illness of nondepressed patients with these conditions.

*

Buchwald D, Pascualy R, Bombardier C, Kith P. Sleep disorders in patients with chronic fatigue. *Clin Infect Dis.* 1994 Jan;18 Suppl 1:S68-72. PMID: 8148456

Study results suggest that patients who qualify for CFS diagnoses may have sleep disorders that, while they don't cause the disease, may improve with treatment.

*

Krupp LB, Jandorf L, Coyle PK, Mendelson WB. Sleep disturbance in chronic fatigue syndrome. *J Psychosom Res.* 1993 May;37(4):325-31. PMID: 8510058

Subjective sleep disturbance is common in CFS and some CFS patients may have objective sleep disorders.

*

Morriss R, Sharpe M, Sharpley AL, Cowen PJ, Hawton K, Morris J. Abnormalities of sleep in patients with the chronic fatigue syndrome. *BMJ.* 1993 May 1;306(6886):1161-4. PMID: 8499816

Most people in a group of CFS patients had sleep disorders, which are likely to contribute to daytime fatigue.

Pain

Nijs J, Van de Putte K, Louckx F, Truijen S, De Meirleir K. Exercise performance and chronic pain in chronic fatigue syndrome: the role of pain catastrophizing. *Pain Med.* 2008 Nov;9(8):1164-72. PMID: 19086101

There is an association between "pain catastrophizing," bodily pain, exercise performance, and self-reported disability in female patients with CFS who experience widespread pain.

*

Meeus M, Nijs J, Van de Wauwer N, Toeback L, Truijen S. Diffuse noxious inhibitory control is delayed in chronic fatigue syndrome: an experimental study. *Pain.* 2008 Oct 15;139(2):439-48. PMID: 18617327

Delayed pain inhibition may play a role in chronic widespread pain in CFS.

*

Ullrich PM, Afari N, Jacobsen C, Goldberg J, Buchwald D. Cold pressor pain sensitivity in monozygotic twins discordant for chronic fatigue syndrome. *Pain Med.* 2007 Apr;8(3):216-22. PMID: 17371408

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Although cold pain threshold and tolerance levels were slightly lower in twins with CFS than their cotwins without CFS, these differences failed to reach statistical significance. Subjective ratings of pain and fatigue at multiple time points during the experimental protocol among twins with CFS were significantly higher than ratings of pain ($P = 0.003$) and fatigue ($P < 0.001$) by their cotwins without CFS.

*

Meeus M, Nijs J, Meirleir KD. Chronic musculoskeletal pain in patients with the chronic fatigue syndrome: a systematic review. *Eur J Pain*. 2007 May;11(4):377-86. PMID: 16843021

Chronic pain is important in CFS and needs to be studied more.

*

Geisser ME, Gracely RH, Giesecke T, Petzke FW, Williams DA, Clauw DJ. The association between experimental and clinical pain measures among persons with fibromyalgia and chronic fatigue syndrome. *Eur J Pain*. 2007 Feb;11(2):202-7. PMID: 16546424

CFS patients' responses to painful experimental stimuli were measured.

Muscles

Nijs J, Aelbrecht S, Meeus M, Van Oosterwijck J, Zinzen E, Clarys P. Tired of being inactive: a systematic literature review of physical activity, physiological exercise capacity and muscle strength in patients with chronic fatigue syndrome. *Disabil Rehabil*. 2011;33(17-18):1493-500. PMID: 21166613

Patients have less peak isometric muscle strength compared to healthy sedentary control subjects.

*

Light AR, Vierck CJ, Light KC. Myalgia and Fatigue: Translation from Mouse Sensory Neurons to Fibromyalgia and Chronic Fatigue Syndromes. In: *Translational Pain Research: From Mouse to Man*. Kruger L, Light AR, editors. Boca Raton, FL: CRC Press; 2010. Chapter 11. PMID: 21882454

The authors suggest that there is a simpler sensation of fatigue that is triggered by inputs from specific receptors that are sensitive to metabolites produced by muscle contraction. They propose that this elementary sensation is transduced, conducted, and perceived within a unique sensory system with properties analogous to other sensory modalities such as pain, and call it the "sensation of muscle fatigue."

*

Pietrangelo T, Toniolo L, Paoli A, Fulle S, Puglielli C, Fanò G, Reggiani C. Functional characterization of muscle fibres from patients with chronic fatigue syndrome: case- control study. *Int J Immunopathol Pharmacol*. 2009 Apr-Jun;22(2):427-36. PMID:19505395

This study supports the view that muscle tissue is directly involved in the pathogenesis of CSF and it might contribute to the early onset of fatigue typical of the skeletal muscles of CFS patients.

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McCully KK, Natelson BH, Iotti S, Sisto S, Leigh JS Jr. Reduced oxidative muscle metabolism in chronic fatigue syndrome. *Muscle Nerve*. 1996 May;19(5):621-5. PMID: 8618560

Oxidative metabolism is reduced in CFS patients compared to sedentary controls.

*

Preedy VR, Smith DG, Salisbury JR, Peters TJ. Biochemical and muscle studies in patients with acute onset post-viral fatigue syndrome. *J Clin Pathol*. 1993 Aug;46(8):722-6. PMID: 7691895

Patients with acute onset post viral fatigue syndrome lose muscle protein synthetic potential, but not muscle bulk.

*

Connolly S, Smith DG, Doyle D, Fowler CJ. Chronic fatigue: electromyographic and neuropathological evaluation. *J Neurol*. 1993 Jul;240(7):435-8. PMID: 8410086

Muscle fibre density estimation may be a useful way of identifying a subgroup of CFS sufferers with a possible primary muscle disorder.

*

Behan WM, More IA, Behan PO. Mitochondrial abnormalities in the postviral fatigue syndrome. *Acta Neuropathol*. 1991;83(1):61-5. PMID:1792865

Muscle biopsies of patients with postviral fatigue syndrome showed mild to severe atrophy of type II fibres in 39 biopsies, with a mild to moderate excess of lipid. On ultrastructural examination, 35 of these specimens showed branching and fusion of mitochondrial cristae. Mitochondrial degeneration was obvious in 40 of the biopsies with swelling, vacuolation, myelin figures and secondary lysosomes.

Physical Symptoms

Hutchinson CV, Maltby J, Badham SP, Jason LA. Vision-related symptoms as a clinical feature of chronic fatigue syndrome/myalgic encephalomyelitis? Evidence from the DePaul Symptom Questionnaire. *Br J Ophthalmol*. 2014 Jan;98(1):144-5. PMID: 24187048

People diagnosed with CFS/ME consistently report that they experience vision-related symptoms associated with their illness.

*

Rayhan RU, Ravindran MK, Baraniuk JN. Migraine in gulf war illness and chronic fatigue syndrome: prevalence, potential mechanisms, and evaluation. *Front Physiol*. 2013 Jul 24;4:181. PMID: 23898301

The high prevalence of migraine in CFS was confirmed and extended to GWI subjects.

Appendix of Comments

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Ravindran M, Adewuyi O, Zheng Y, Rayhan RU, Le U, Timbol C, Merck S, Esteitie R, Read C, Cooney M, Baraniuk J. Dyspnea in Chronic Fatigue Syndrome (CFS): comparison of two prospective cross-sectional studies. *Glob J Health Sci.* 2012 Dec 12;5(2):94-110. PMID: 23445698

This study showed that a much higher percentage of CFS patients than healthy controls significant dyspnea (shortness of breath).

*

Ravindran MK, Zheng Y, Timbol C, Merck SJ, Baraniuk JN. Migraine headaches in Chronic Fatigue Syndrome (CFS): Comparison of two prospective cross-sectional studies. *BMC Neurol.* 2011 Mar 5;11:30. PMID: 21375763

CFS patients have a higher prevalence of migraine headaches (with and without aura) than healthy controls.

*

Boneva RS, Maloney EM, Lin JM, Jones JF, Wieser F, Nater UM, Heim CM, Reeves WC. Gynecological history in chronic fatigue syndrome: a population-based case-control study. *J Womens Health (Larchmt).* 2011 Jan;20(1):21-8. PMID: 21091051

A greater proportion of women with CFS than controls reported pelvic pain unrelated to menstruation, endometriosis, and periods of amenorrhea. Compared to controls, women in the CFS group had a higher mean number of pregnancies and gynecological surgeries. Among menopausal women, 76% of the CFS group reported hysterectomy vs. 54.6% of controls, and 56% of women with CFS reported oophorectomy vs. 34.3% of controls.

*

Nickel JC, Tripp DA, Pontari M, Moldwin R, Mayer R, Carr LK, Doggweiler R, Yang CC, Mishra N, Nordling J. Interstitial cystitis/painful bladder syndrome and associated medical conditions with an emphasis on irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome. *J Urol.* 2010 Oct;184(4):1358-63. PMID: 20719340

CFS and interstitial cystitis/painful bladder syndrome are related.

*

Baraniuk JN, Zheng Y. Relationships among rhinitis, fibromyalgia, and chronic fatigue. *Allergy Asthma Proc.* 2010 May-Jun;31(3):169-78. PMID: 20615318

There is a high prevalence of idiopathic nonallergic rhinopathy in CFS. CFS also has significant overlap with systemic hyperalgesia (fibromyalgia), autonomic dysfunction (irritable bowel syndrome and migraine headaches), sensory hypersensitivity (dyspnea; congestion; rhinorrhea; and appreciation of visceral nociception in the esophagus, gastrointestinal tract, bladder, and other organs), and central nervous system maladaptations (central sensitization) recorded by functional magnetic resonance imaging (fMRI). Neurological dysfunction may account for the overlap of CFS with idiopathic nonallergic rhinopathy.

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Maloney EM, Boneva RS, Lin JM, Reeves WC. Chronic fatigue syndrome is associated with metabolic syndrome: results from a case-control study in Georgia. *Metabolism*. 2010 Sep;59(9):1351-7. PMID: 20102774

CFS was associated with metabolic syndrome, which further exacerbated fatigue.

*

Meeus M, Nijs J, Huybrechts S, Truijen S. Evidence for generalized hyperalgesia in chronic fatigue syndrome: a case control study. *Clin Rheumatol*. 2010 Apr;29(4):393-8. PMID: 20077123

CFS patients exhibited more generalized hyperalgesia than controls.

*

Blazquez A, Alegre J, Ruiz E. Women with chronic fatigue syndrome and sexual dysfunction: past, present, and future. *J Sex Marital Ther*. 2009 Oct;35(5):347-59. PMID: 20183003

Sexual dysfunction is a problem experienced by patients with chronic fatigue syndrome (CFS).

*

Jhanji V, Beltz J, Vajpayee RB. Contact lens-related acanthamoeba keratitis in a patient with chronic fatigue syndrome. *Eye Contact Lens*. 2008 Nov;34(6):335-6. PMID: 18997544

Contact lens-related Acanthamoeba keratitis was diagnosed in a 58-year-old man with a history of CFS. After medical management failed to prevail, a penetrating keratoplasty was performed in the affected eye.

*

Fisher MM, Rose M. Anaesthesia for patients with idiopathic environmental intolerance and chronic fatigue syndrome. *Br J Anaesth*. 2008 Oct;101(4):486-91. PMID: 18782886

Anaesthesia is likely to be associated with adverse effects in CFS patients but the effects are not likely to be severe.

*

Wyller VB, Godang K, Mørkrid L, Saul JP, Thaulow E, Walløe L. Abnormal thermoregulatory responses in adolescents with chronic fatigue syndrome: relation to clinical symptoms. *Pediatrics*. 2007 Jul;120(1):e129-37. PMID: 17606539

Adolescent patients with chronic fatigue syndrome have abnormal catecholaminergic-dependent thermoregulatory responses, suggesting sympathetic dysfunction and possibly.

*

Bennett B, Goldstein D, Friedlander M, Hickie I, Lloyd A. The experience of cancer-related fatigue and chronic fatigue syndrome: a qualitative and comparative study. *J Pain Symptom Manage*. 2007 Aug;34(2):126-35. PMID: 17544246

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Qualitatively, cancer related fatigue appears closely related to CFS.

*

Nijs J, Aerts A, De Meirleir K. Generalized joint hypermobility is more common in chronic fatigue syndrome than in healthy control subjects. *J Manipulative Physiol Ther.* 2006 Jan;29(1):32-9. PMID: 16396727

CFS patients were more likely than controls to have joint hypermobility.

*

van de Putte EM, Uiterwaal CS, Bots ML, Kuis W, Kimpen JL, Engelbert RH. Is chronic fatigue syndrome a connective tissue disorder? A cross-sectional study in adolescents. *Pediatrics.* 2005 Apr;115(4):e415-22. PMID: 15805343

Patients with CFS had lower blood pressure, stiffer arteries and more extensible skin, but did not have joint hypermobility.

*

Ferré Ybarz L, Cardona Dahl V, Cadahía García A, Ruiz E, Vázquez A, Fernández de Sevilla T, Alegre Martín J. Prevalence of atopy in chronic fatigue syndrome. *Allergol Immunopathol (Madr).* 2005 Jan-Feb;33(1):42-7. PMID: 15777523

Atopy was not more prevalent in patients with CFS than in healthy controls, although the CFS group tended to report more respiratory symptoms and drug allergies.

*

Shee CD. Phantom lymphadenopathy. An association with chronic fatigue syndrome. *Postgrad Med J.* 2003 Jan;79(927):59-60. PMID: 12566557

Phantom lymphadenopathy may be a symptom in some people with CFS.

*

Jason LA, Torres-Harding SR, Carrico AW, Taylor RR. Symptom occurrence in persons with chronic fatigue syndrome. *Biol Psychol.* 2002 Feb;59(1):15-27. PMID: 11790441

Headaches, lymph node pain, sore throat, joint pain, muscle pain, muscle weakness at multiple sites differentiate CFS patients from controls. The disease includes many cardiopulmonary, neurological, and other symptoms not included in the CDC case definition.

*

Barron DF, Cohen BA, Geraghty MT, Violand R, Rowe PC. Joint hypermobility is more common in children with chronic fatigue syndrome than in healthy controls. *J Pediatr.* 2002 Sep;141(3):421-5. PMID: 12219066

Joint hypermobility is more common in patients with CFS than in otherwise healthy children with common skin disorders.

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Baraniuk JN, Clauw DJ, Gaumont E. Rhinitis symptoms in chronic fatigue syndrome. *Ann Allergy Asthma Immunol.* 1998 Oct;81(4):359-65. PMID: 9809501

In a CFS population, 24% had no significant rhinitis complaints, 30% had positive skin tests suggesting the potential for allergic rhinitis complaints, and 46% had nonallergic rhinitis.

*

Harlow BL, Signorello LB, Hall JE, Dailey C, Komaroff AL. Reproductive correlates of chronic fatigue syndrome. *Am J Med.* 1998 Sep 28;105(3A):945-99S. PMID: 9790489

Women with CFS reported increased gynecologic complications, a lower incidence of premenstrual symptomatology. Issues included self-reported irregular cycles, periods of amenorrhea, sporadic bleeding between menstrual periods, and factors suggestive of abnormal ovarian function (such as a history of polycystic ovarian syndrome, hirsutism, and ovarian cysts).

*

Gomborone JE, Gorard DA, Dewsnap PA, Libby GW, Farthing MJ. Prevalence of irritable bowel syndrome in chronic fatigue. *J R Coll Physicians Lond.* 1996 Nov-Dec;30(6):512-3. PMID: 8961203

63% of people belonging to a group for chronic fatigue sufferers fulfilled a diagnosis of irritable bowel syndrome (recurrent abdominal pain and at least three Manning criteria). This greatly exceeds estimates of irritable bowel syndrome prevalence of up to 22% in the general population.

*

Buchwald D, Umali P, Umali J, Kith P, Pearlman T, Komaroff AL. Chronic fatigue and the chronic fatigue syndrome: prevalence in a Pacific Northwest health care system. *Ann Intern Med.* 1995 Jul 15;123(2):81-8. PMID: 7778839

People with CFS had more frequent cervical and axillary adenopathy, poorer functional status, and greater psychological distress than controls.

*

Sisto SA, Tapp W, Drastal S, Bergen M, DeMasi I, Cordero D, Natelson B. Vagal tone is reduced during paced breathing in patients with the chronic fatigue syndrome. *Clin Auton Res.* 1995 Jun;5(3):139-43. PMID: 7549414

Vagal power was significantly lower in a CFS group versus healthy controls.

*

Caffery BE, Josephson JE, Samek MJ. The ocular signs and symptoms of chronic fatigue syndrome. *J Am Optom Assoc.* 1994 Mar;65(3):187-91. PMID: 8201170

Significant ocular symptoms were present in all 25 of a group of CFS patients. The most common clinical findings were abnormalities of the preocular tear film and ocular surface and reduced accommodation for age.

*

Saisch SG, Deale A, Gardner WN, Wessely S. Hyperventilation and chronic fatigue syndrome. *Q J Med.*

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1994 Jan;87(1):63-7. PMID: 8140219

The authors found a weak association between hyperventilation and chronic fatigue syndrome.

*

Auger PL, Gourdeau P, Miller JD. Clinical experience with patients suffering from a chronic fatigue-like syndrome and repeated upper respiratory infections in relation to airborne molds. *Am J Ind Med.* 1994 Jan;25(1):41-2. PMID: 8116649

*

Potaznick W, Kozol N. Ocular manifestations of chronic fatigue and immune dysfunction syndrome. *Optom Vis Sci.* 1992 Oct;69(10):811-4. PMID: 1437004

CFS patients are especially likely to report a wide variety of eye problems.

*

Cunha BA. Crimson crescents--a possible association with the chronic fatigue syndrome. *Ann Intern Med.* 1992 Feb 15;116(4):347. PMID: 1733396

A particular pattern of redness in the throat may be related to CFS.

Physical Abnormalities

Chen CS, Lin WM, Yang TY, Chen HJ, Kuo CN, Kao CH. Chronic fatigue syndrome is associated with the risk of fracture: a nationwide cohort study. *QJM.* 2014 Mar 13. PMID: 24619129

Researchers used the National Health Insurance Research Database in Taiwan to conduct a prospective cohort study, identifying 3744 patients with a CFS diagnosis and 14,976 patients without CFS. The incidence rate of fracture was higher in the CFS cohort than in the non-CFS cohort.

*

Badham SP, Hutchinson CV. Characterising eye movement dysfunction in myalgic encephalomyelitis/chronic fatigue syndrome. *Graefes Arch Clin Exp Ophthalmol.* 2013 Aug 6. PMID: 23918092

ME/CFS patients showed relatively intact ability to accurately fixate the target (prosaccades), but were impaired when required to focus accurately in a specific position opposite the target (antisaccades). Patients were most markedly impaired when required to direct their gaze as closely as possible to a smoothly moving target (smooth pursuit).

*

Hutchinson CV, Badham SP. Patterns of abnormal visual attention in myalgic encephalomyelitis. *Optom Vis Sci.* 2013 Jun;90(6):607-14. PMID: 23689679

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Patients and controls performed similarly on the processing speed subtest of the Useful Field of View. However, patients exhibited marginally worse performance compared with controls on the divided attention subtest and significantly worse performance on the

selective attention subtest. In the spatial cueing task, they were slower than controls to respond to the presence of the target, particularly when cues were invalid. They were also impaired, relative to controls, on visual search tasks.

*

He J, Hollingsworth KG, Newton JL, Blamire AM. Cerebral vascular control is associated with skeletal muscle pH in chronic fatigue syndrome patients both at rest and during dynamic stimulation. *Neuroimage Clin.* 2013 Jan 5;2:168-73. PMID: 24179772

The researchers found that cerebral vascular control is closely related to skeletal muscle pH both at rest and after dynamic stimulation in CFS.

*

Sakudo A, Kuratsune H, Kato YH, Ikuta K. Visible and near-infrared spectra collected from the thumbs of patients with chronic fatigue syndrome for diagnosis. *Clin Chim Acta.* 2012 Oct 9;413(19-20):1629-32. PMID: 22583968

Visible and near-infrared spectroscopy of the thumb combined with chemometrics analysis may provide a valuable tool for diagnosing CFS.

*

Newton DJ, Kennedy G, Chan KK, Lang CC, Belch JJ, Khan F. Large and small artery endothelial dysfunction in chronic fatigue syndrome. *Int J Cardiol.* 2011 Nov 10. PMID: 22078396

Endothelial dysfunction is present in CFS.

*

Ohashi K, Bleijenberg G, van der Werf S, Prins J, Amaral LA, Natelson BH, Yamamoto Y. Decreased fractal correlation in diurnal physical activity in chronic fatigue syndrome. *Methods Inf Med.* 2004;43(1):26-9. PMID: 15026831

CFS patients had more abrupt interruptions of voluntary physical activity during diurnal periods in normal daily life, probed by the decreased correlation in the negative modulus maxima of the wavelet-transformed activity data, possibly due to their exaggerated fatigue.

*

Gordon R, Michalewski HJ, Nguyen T, Gupta S, Starr A. Cortical motor potential alterations in chronic fatigue syndrome. *Int J Mol Med.* 1999 Nov;4(5):493-9. PMID: 10534571

CFS patients have slowed reaction times reduced premovement-related potentials, suggesting that central motor mechanisms accompanying motor response preparation were impaired in CFS for some tasks.

*

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Servatius RJ, Tapp WN, Bergen MT, Pollet CA, Drastal SD, Tiersky LA, Desai P, Natelson BH. Impaired associative learning in chronic fatigue syndrome. *Neuroreport*. 1998 Apr 20;9(6):1153-7. PMID: 9601685

CFS patients displayed impaired acquisition of the eyeblink response using a delayed- type conditioning paradigm. This suggests organic brain dysfunction within a defined neural substrate in CFS patients.

*

Ash-Bernal R, Wall C 3rd, Komaroff AL, Bell D, Oas JG, Payman RN, Fagioli LR. Vestibular function test anomalies in patients with chronic fatigue syndrome. *Acta Otolaryngol*. 1995 Jan;115(1):9-17. PMID: 7762393

Researchers performed vestibular function testing performed on 11 CFS patients and concluded that results are more suggestive of central nervous system deficits than of peripheral vestibular dysfunction.

Laboratory Abnormalities

Brewer JH, Thrasher JD, Straus DC, Madison RA, Hooper D. Detection of mycotoxins in patients with chronic fatigue syndrome. *Toxins (Basel)*. 2013 Apr 11;5(4):605-17. PMID: 23580077

Urine specimens from 104 of 112 CFS patients (93%) were positive for at least one mycotoxin. Ochratoxin A was detected in 83% of samples and macrocyclic trichothecenes were detected in 44%.

*

Ciregia F, Giusti L, Da Valle Y, Donadio E, Consensi A, Giacomelli C, Sernissi F, Scarpellini P, Maggi F, Lucacchini A, Bazzichi L. A multidisciplinary approach to study a couple of monozygotic twins discordant for the chronic fatigue syndrome: a focus on potential salivary biomarkers. *J Transl Med*. 2013 Oct 2;11:243. PMID: 24088505

This study shows the presence of differentially expressed proteins in the saliva of the couple of monozygotic twins discordant for CFS, probably related to the disease.

*

Klimas NG, Broderick G, Fletcher MA. Biomarkers for chronic fatigue. *Brain Behav Immun*. 2012 Nov;26(8):1202-10. PMID: 22732129

This review is focused on the recent literature related to biomarkers for fatigue associated with CFS/ME and, for comparison, those associated with other diseases.

*

Medow MS, Aggarwal A, Baugham I, Messer Z, Stewart JM. Modulation of the axon-reflex response to local heat by reactive oxygen species in subjects with chronic fatigue syndrome. *J Appl Physiol*. 2013 Jan 1;114(1):45-51. PMID: 23139367

The response to local cutaneous heating may be altered by local levels of ROS, particularly H₂O₂ in

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CFS subjects, and may be related to their hyperesthesia/hyperalgesia.

*

Stringer EA, Baker KS, Carroll IR, Montoya JG, Chu L, Maecker HT, Younger JW. Daily cytokine fluctuations, driven by leptin, are associated with fatigue severity in chronic fatigue syndrome: evidence of inflammatory pathology. *J Transl Med.* 2013 Apr 9;11:93. PMID: 23570606

Self-reported fatigue severity was significantly correlated with leptin levels in six out of 10 CFS patients and one out of 10 healthy control.

*

Fukuda S, Horiguchi M, Yamaguti K, Nakatomi Y, Kuratsune H, Ichinose H, Watanabe Y. Association of monoamine-synthesizing genes with the depression tendency and personality in chronic fatigue syndrome patients. *Life Sci.* 2013 Feb 27;92(3):183-6. PMID: 23246742

The study results suggest that the biosynthetic pathways of the monoamine neurotransmitters that are mediated by tyrosine hydroxylase and GTP cyclohydrolase I might be associated with the CFS clinical findings.

Maes M, Ringel K, Kubera M, Anderson G, Morris G, Galecki P, Geffard M. In myalgic encephalomyelitis/chronic fatigue syndrome, increased autoimmune activity against 5-HT is associated with immuno-inflammatory pathways and bacterial translocation. *J Affect Disord.* 2013 May 9. PMID: 23664637

The study's results show that, in ME/CFS, increased serotonin (5-HT) autoimmune activity is associated with activation of immuno-inflammatory pathways and increased bacterial translocation, factors which are known to play a role in the onset of autoimmune reactions.

*

Tomic S, Brkic S, Maric D, Mikic AN. Lipid and protein oxidation in female patients with chronic fatigue syndrome. *Arch Med Sci.* 2012 Nov 9;8(5):886-91. PMID: 23185200

A group of CFS patients had higher levels of triglycerides, malondialdehyde and protein oxidation protein carbonyl and lower levels of HDL cholesterol than the control group. This suggests an unfavorable lipid profile and signs of oxidative stress induced damage to lipids and proteins.

*

Armstrong CW, McGregor NR, Sheedy JR, Buttfield I, Butt HL, Gooley PR. NMR metabolic profiling of serum identifies amino acid disturbances in chronic fatigue syndrome. *Clin Chim Acta.* 2012 Oct 9;413(19-20):1525-31. PMID: 22728138

This study's results showed a significant reduction of glutamine and ornithine in the blood of the CFS samples. Correlation analysis of glutamine and ornithine with other metabolites in the CFS sera showed relationships with glucogenic amino acids and metabolites that participate in the urea cycle. This indicates a possible disturbance to amino acid and nitrogen metabolism.

*

Shungu DC, Weiduschat N, Murrrough JW, Mao X, Pillemer S, Dyke JP, Medow MS, Natelson BH, Stewart JM, Mathew SJ. Increased ventricular lactate in chronic fatigue syndrome. III. Relationships to

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cortical glutathione and clinical symptoms implicate oxidative stress in disorder pathophysiology. *NMR Biomed.* 2012 Sep;25(9):1073-87. PMID: 22281935

In two previous reports, the researchers found significantly higher levels of ventricular cerebrospinal fluid (CSF) lactate in patients with CFS relative to those with generalized anxiety disorder and healthy volunteers (HV), but not relative to those with major depressive disorder (MDD). In this new study, they found elevated ventricular lactate and decreased GSH in patients with CFS and MDD relative to HVs. Collectively, the results

of this third independent study support a pathophysiological model of CFS in which increased oxidative stress may play a key role in CFS etiopathophysiology.

*

Murrough JW, Mao X, Collins KA, Kelly C, Andrade G, Nestadt P, Levine SM, Mathew SJ, Shungu DC. Increased ventricular lactate in chronic fatigue syndrome measured by ¹H MRS imaging at 3.0 T. II: comparison with major depressive disorder. *NMR Biomed.* 2010 Jul;23(6):643-50. PMID: 20661876

Ventricular CSF lactate was significantly elevated in CFS compared to healthy volunteers. There was a significant correlation between ventricular CSF lactate and severity of mental fatigue that was specific to the CFS group.

*

Schutzer SE, Angel TE, Liu T, Schepmoes AA, Clauss TR, Adkins JN, Camp DG, Holland BK, Bergquist J, Coyle PK, Smith RD, Fallon BA, Natelson BH. Distinct cerebrospinal fluid proteomes differentiate post-treatment Lyme disease from chronic fatigue syndrome. *PLoS One.* 2011 Feb 23;6(2):e17287. PMID: 21383843

Analysis of cerebral spinal fluids accurately distinguished CFS, Chronic Lyme and healthy subjects, and thus has potential as a biomarker.

*

Fletcher MA, Rosenthal M, Antoni M, Ironson G, Zeng XR, Barnes Z, Harvey JM, Hurwitz B, Levis S, Broderick G, Klimas NG. Plasma neuropeptide Y: a biomarker for symptom severity in chronic fatigue syndrome. *Behav Brain Funct.* 2010 Dec 29;6:76. PMID: 21190576

Plasma Neuropeptide Y is elevated in CFS patients compared to healthy controls and to a fatigued comparison group, GWI patients.

*

Raison CL, Lin JM, Reeves WC. Association of peripheral inflammatory markers with chronic fatigue in a population-based sample. *Brain Behav Immun.* 2009 Mar;23(3):327-37. PMID: 19111923

CFS patients as well as patients with general fatigue had abnormally elevated levels of plasma concentrations of high-sensitivity c-reactive protein (hs-CRP).

Sakudo A, Kato YH, Tajima S, Kuratsune H, Ikuta K. Visible and near-infrared spectral changes in the thumb of patients with chronic fatigue syndrome. *Clin Chim Acta.* 2009 May;403(1-2):163-6. PMID: 19248775

CFS patients have a variety of problems with their blood, including a decrease in water content and increases in oxyhemoglobin content, oxidation of heme a+a(3) and copper in cytochrome c oxidase.

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Sakudo A, Kuratsune H, Kato YH, Ikuta K. Secondary structural changes of proteins in fingernails of chronic fatigue syndrome patients from Fourier-transform infrared spectra. *Clin Chim Acta*. 2009 Apr;402(1-2):75-8. PMID: 19150612

The fingernails of CF patients showed a decreased alpha-helix content and an increased beta-sheet content, suggesting reduced levels of normal elements in the nail plate.

*

Chen R, Moriya J, Yamakawa J, Takahashi T, Li Q, Morimoto S, Iwai K, Sumino H, Yamaguchi N, Kanda T. Brain atrophy in a murine model of chronic fatigue syndrome and beneficial effect of Hochu-ekki-to (TJ-41). *Neurochem Res*. 2008 Sep;33(9):1759-67. PMID: 18317925

In a mouse model of CFS, brain-derived neurotrophic factor (BDNF) and Bcl-2 mRNA expression levels in the hippocampus were suppressed.

*

Niblett SH, King KE, Dunstan RH, Clifton-Bligh P, Hoskin LA, Roberts TK, Fulcher GR, McGregor NR, Dunsmore JC, Butt HL, Klineberg I, Rothkirch TB. Hematologic and urinary excretion anomalies in patients with chronic fatigue syndrome. *Exp Biol Med (Maywood)*. 2007 Sep;232(8):1041-9. PMID: 17720950

CFS patients display abnormalities in a variety of blood and urine tests.

*

Nishikai M. Antinuclear antibodies in patients with chronic fatigue syndrome. *Nihon Rinsho*. 2007 Jun;65(6):1067-70. PMID: 17561698

Anti-68/48kD protein autoantibodies were found in 13% of 114 CFS patients and 0% in healthy subjects ($p < 0.05$). Hypersomnia and difficulty in concentration were found more frequently in the CFS patients with this specific autoantibody.

*

Miwa S, Takikawa O. Chronic fatigue syndrome and neurotransmitters. *Nihon Rinsho*. 2007 Jun;65(6):1005-10. PMID: 17561689

Studies suggest that CFS is closely associated with attenuation of central synaptic transmission mediated by neurotransmitters such as serotonin and glutamate.

*

Hannestad U, Theodorsson E, Evengård B. beta-Alanine and gamma-aminobutyric acid in chronic fatigue syndrome. *Clin Chim Acta*. 2007 Feb;376(1-2):23-9. PMID: 16934791

Increased excretion of beta-alanine was found in a subgroup of CFS patients.

*

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Sakudo A, Kuratsune H, Kobayashi T, Tajima S, Watanabe Y, Ikuta K. Spectroscopic diagnosis of chronic fatigue syndrome by visible and near-infrared spectroscopy in serum samples. *Biochem Biophys Res Commun*. 2006 Jul 14;345(4):1513-6. PMID: 16730652

Vis-NIR spectroscopy for sera combined with chemometrics analysis could provide a promising tool to objectively diagnose CFS.

*

Cleare AJ, Messa C, Rabiner EA, Grasby PM. Brain 5-HT_{1A} receptor binding in chronic fatigue syndrome measured using positron emission tomography and [¹¹C]WAY-100635. *Biol Psychiatry*. 2005 Feb 1;57(3):239-46. PMID: 15691524

There is evidence of decreased 5-HT_{1A} receptor number or affinity in CFS.

*

Baraniuk JN, Casado B, Maibach H, Clauw DJ, Pannell LK, Hess S S. A Chronic Fatigue Syndrome - related proteome in human cerebrospinal fluid. *BMC Neurol*. 2005 Dec 1;5:22. PMID: 16321154

This pilot study detected an identical set of central nervous system, innate immune and amyloidogenic proteins in cerebrospinal fluids from two independent cohorts of subjects with overlapping CFS, PGI and fibromyalgia.

*

Casado B, Zanone C, Annovazzi L, Iadarola P, Whalen G, Baraniuk JN. Urinary electrophoretic profiles from chronic fatigue syndrome and chronic fatigue syndrome/fibromyalgia patients: a pilot study for achieving their normalization. *J*

Chromatogr B Analyt Technol Biomed Life Sci. 2005 Jan 5;814(1):43-51. PMID: 15607706

CFS/fibromyalgia and CFS had significant differences in urine compared to normal controls that may be of significance as biomarkers of illnesses.

*

Natelson BH, Weaver SA, Tseng CL, Ottenweller JE. Spinal fluid abnormalities in patients with chronic fatigue syndrome. *Clin Diagn Lab Immunol*. 2005 Jan;12(1):52-5. PMID: 15642984

Significantly more CFS patients had elevations in spinal fluid in either protein levels or number of cells than healthy controls.

*

Yamamoto S, Ouchi Y, Onoe H, Yoshikawa E, Tsukada H, Takahashi H, Iwase M, Yamaguti K, Kuratsune H, Watanabe Y. Reduction of serotonin transporters of patients with chronic fatigue syndrome. *Neuroreport*. 2004 Dec 3;15(17):2571-4. PMID: 15570154

The density of serotonin transporters (5-HTTs) in the brain, as determined by using a radiotracer, [³H](+)-McN5652, was significantly reduced in the rostral subdivision of the anterior cingulate of CFS patients as compared with that in normal volunteers.

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Spence VA, Khan F, Kennedy G, Abbot NC, Belch JJ. Acetylcholine mediated vasodilatation in the microcirculation of patients with chronic fatigue syndrome. *Prostaglandins Leukot Essent Fatty Acids*. 2004 Apr;70(4):403-7. PMID: 15041034

Most diseases are accompanied by a blunted response to acetylcholine but the opposite is true for CFS. Such sensitivity is normally associated with physical training so the finding in CFS is anomalous and may well be relevant to vascular symptoms that characterise many patients. There are several mechanisms that might lead to ACh endothelial sensitivity in CFS patients.

*

McCully KK, Smith S, Rajaei S, Leigh JS Jr, Natelson BH. Muscle metabolism with blood flow restriction in chronic fatigue syndrome. *J Appl Physiol*. 2004 Mar;96(3):871-8. PMID: 14578362

CFS patients showed evidence of reduced hyperemic flow and reduced oxygen delivery but no evidence that this impaired muscle metabolism.

Nijs J, De Becker P, De Meirleir K, Demanet C, Vincken W, Schuermans D, McGregor N. Associations between bronchial hyperresponsiveness and immune cell parameters in patients with chronic fatigue syndrome. *Chest*. 2003 Apr;123(4):998-1007. PMID: 12684286

CFS patients have chronic immune activation, compared to normal people. Bronchial hyperresponsiveness is associated with that.

*

Tanaka S, Kuratsune H, Hidaka Y, Hakariya Y, Tatsumi KI, Takano T, Kanakura Y, Amino N. Autoantibodies against muscarinic cholinergic receptor in chronic fatigue syndrome. *Int J Mol Med*. 2003 Aug;12(2):225-30. PMID: 12851722

Subgroups of CFS are associated with autoimmune abnormalities of CHRM1.

*

Narita M, Nishigami N, Narita N, Yamaguti K, Okado N, Watanabe Y, Kuratsune H. Association between serotonin transporter gene polymorphism and chronic fatigue syndrome. *Biochem Biophys Res Commun*. 2003 Nov 14;311(2):264-6. PMID: 14592408

Attenuated concentration of extracellular serotonin due to longer variants may cause higher susceptibility to CFS.

*

Puri BK, Counsell SJ, Zaman R, Main J, Collins AG, Hajnal JV, Davey NJ. Relative increase in choline in the occipital cortex in chronic fatigue syndrome. *Acta Psychiatr Scand*. 2002 Sep;106(3):224-6. PMID: 12197861

The mean ratio of choline to creatine in the occipital cortex in CFS was significantly higher than in the controls. Our results suggest that there may be an abnormality of phospholipid metabolism in the brain in CFS.

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Panerai AE, Vecchiet J, Panzeri P, Meroni P, Scarone S, Pizzigallo E, Giamberardino MA, Sacerdote P. Peripheral blood mononuclear cell beta-endorphin concentration is decreased in chronic fatigue syndrome and fibromyalgia but not in depression: preliminary report. *Clin J Pain*. 2002 Jul-Aug;18(4):270-3. PMID: 12131069

Beta-endorphin concentrations were significantly lower in patients with chronic fatigue syndrome or fibromyalgia syndrome than in normal subjects and depressed patients.

Evaluation of peripheral blood mononuclear cell beta-endorphin concentrations could represent a diagnostic tool for chronic fatigue syndrome.

*

Nishikai M, Tomomatsu S, Hankins RW, Takagi S, Miyachi K, Kosaka S, Akiya K. Autoantibodies to a 68/48 kDa protein in chronic fatigue syndrome and primary fibromyalgia: a possible marker for hypersomnia and cognitive disorders. *Rheumatology (Oxford)*. 2001 Jul;40(7):806-10. PMID: 11477286

The presence of the anti-68/48 kDa protein antibodies in a portion of both CFS and primary FM patients suggests the existence of a common immunological background. These antibodies may find utility as possible markers for a clinicoserological subset of CFS/FM patients with hypersomnia and cognitive complaints.

*

Woo SB, Schacterle RS, Komaroff AL, Gallagher GT. Salivary gland changes in chronic fatigue syndrome: a case-controlled preliminary histologic study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2000 Jul;90(1):82-7. PMID: 10884641

The salivary gland changes in patients with chronic fatigue syndrome show varying degrees of ductal and acinar dilatation, periductal fibrosis, lymphoplasmacytic infiltrates, and occasional lymphocytic foci, all suggestive of primary gland damage. The one parameter that showed statistical significance was the presence of mast cells.

*

De Meirleir K, Bisbal C, Campine I, De Becker P, Salehzada T, Demette E, Lebleu B. A 37 kDa 2-5A binding protein as a potential biochemical marker for chronic fatigue syndrome. *Am J Med*. 2000 Feb;108(2):99-105. PMID: 11126321

The presence of a 37 kDa 2-5A binding protein in extracts of peripheral blood mononuclear cells may distinguish patients with chronic fatigue syndrome from healthy subjects and those suffering from other diseases.

*

Berg D, Berg LH, Couvaras J, Harrison H. Chronic fatigue syndrome and/or fibromyalgia as a variation of antiphospholipid antibody syndrome: an explanatory model and approach to laboratory diagnosis. *Blood Coagul Fibrinolysis*. 1999 Oct;10(7):435-8. PMID: 10695770

A new lab panel allows testing for diagnosis as well as monitoring for anticoagulation protocols in CFS patients.

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Vojdani A, Lapp CW. Interferon-induced proteins are elevated in blood samples of patients with chemically or virally induced chronic fatigue syndrome. *Immunopharmacol Immunotoxicol.* 1999 May;21(2):175-202. PMID: 10319275

Interferon induced proteins 2-5A Synthetase and Protein Kinase RNA (PKR) are not only biomarkers for viral induction of CFS, but biomarkers to other stressors that include MTBE and Benzene.

*

Conti F, Pittoni V, Sacerdote P, Priori R, Meroni PL, Valesini G. Decreased immunoreactive beta-endorphin in mononuclear leucocytes from patients with chronic fatigue syndrome. *Clin Exp Rheumatol.* 1998 Nov-Dec;16(6):729-32. PMID: 9844768

Patients with CFS were found to have low levels of peripheral blood mononuclear cell beta-endorphin. Beta-endorphin concentrations in PBMC seem to mirror the central nervous system homeostasis of the opioid. Therefore, we would postulate that the fatigue and weakness typical of CFS could be related to low beta-endorphin concentrations at the central nervous system level.

*

von Mikecz A, Konstantinov K, Buchwald DS, Gerace L, Tan EM. High frequency of autoantibodies to insoluble cellular antigens in patients with chronic fatigue syndrome. *Arthritis Rheum.* 1997 Feb;40(2):295-305. PMID: 9041942

The high frequency of autoantibodies to insoluble cellular antigens in CFS represents a unique feature which might help to distinguish CFS from other rheumatic autoimmune diseases.

*

Buchwald D, Wener MH, Pearlman T, Kith P. Markers of inflammation and immune activation in chronic fatigue and chronic fatigue syndrome. *J Rheumatol.* 1997 Feb;24(2):372-6. PMID: 9034999

Compared to control subjects, mean concentrations of C-reactive protein, beta 2- microglobulin, and neopterin were higher in patients with CFS and chronic fatigue. The presence of several markers was highly correlated, suggesting a subset of patients with immune activation.

*

Regland B, Andersson M, Abrahamsson L, Bagby J, Dyrehag LE, Gottfries CG. Increased concentrations of homocysteine in the cerebrospinal fluid in patients with fibromyalgia and chronic fatigue syndrome. *Scand J Rheumatol.* 1997;26(4):301-7. PMID: 9310111

In all the subjects in a group of patients having both CFS and fibromyalgia, the homocysteine (HCY) levels were increased in the cerebrospinal fluid (CSF). There was a significant positive correlation between CSF-HCY levels and fatiguability, and the levels of CSF-B12 correlated significantly with the item of fatiguability and with CPRS-15.

*

Konstantinov K, von Mikecz A, Buchwald D, Jones J, Gerace L, Tan EM. Autoantibodies to nuclear envelope antigens in chronic fatigue syndrome. *J Clin Invest.* 1996 Oct 15;98(8):1888-96. PMID: 8878441

We have identified and partially characterized the autoantibodies in sera of 60 patients with chronic fatigue syndrome. Approximately 52% of CFS patients had sera that were found to react with nuclear

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envelope antigens. Some sera immunoprecipitated the *in vitro* transcription and translation product of a human cDNA clone encoding the nuclear envelope protein lamin B1. The autoantibodies were of the IgG isotype. It thus seems there is an autoimmune component in chronic fatigue syndrome.

*

McGregor NR, Dunstan RH, Zerbes M, Butt HL, Roberts TK, Klineberg IJ. Preliminary determination of the association between symptom expression and urinary metabolites in subjects with chronic fatigue syndrome. *Biochem Mol Med*. 1996 Jun;58(1):85-92. PMID: 8809350

Chronic fatigue syndrome (CFS) patients have a urinary metabolite labeled CFSUM1 with increased incidence ($P < 0.004$) and relative abundance ($P < 0.00003$). The relative abundances of urinary CFSUM1 and beta-alanine were associated with alterations in metabolite excretion and symptom incidence. The strong associations of CFSUM1 and beta-alanine with CFS symptom expression provide a molecular basis for developing an objective test for CFS.

*

Conti F, Magrini L, Priori R, Valesini G, Bonini S. Eosinophil cationic protein serum levels and allergy in chronic fatigue syndrome. *Allergy*. 1996 Feb;51(2):124-7. PMID: 8738520

Eosinophil cationic protein serum levels were significantly higher in CFS patients than in controls. In the CFS population, the prevalence of RAST positivity to one or more allergens was 77%, while no control showed positive RAST.

*

Fischler B, D'Haenen H, Cluydts R, Michiels V, Demets K, Bossuyt A, Kaufman L. Comparison of 99m Tc HMPAO SPECT scan between chronic fatigue syndrome, major depression and healthy controls: an exploratory study of clinical correlates of regional cerebral blood flow. *Neuropsychobiology*. 1996;34(4):175-83. PMID: 9121617

Asymmetry ($R > L$) of tracer uptake at parietotemporal level in the brain is demonstrated in CFS as compared with major depression.

*

Natelson BH, Ellis SP, Braonáin PJ, DeLuca J, Tapp WN. Frequency of deviant immunological test values in chronic fatigue syndrome patients. *Clin Diagn Lab Immunol*. 1995 Mar;2(2):238-40. PMID: 7697537

Of 11 immunological tests done on chronic fatigue syndrome patients and on fatigued controls, the best ones to distinguish them from normals were protein A binding, Raji cell, or C3 or C4. Other tests, including immunoglobulin G subclasses, complement component CH50, interleukin-2, and anticardiolipin antibodies, did not discriminate well among the groups.

*

Hilgers A, Frank J. Chronic fatigue syndrome: immune dysfunction, role of pathogens and toxic agents and neurological and cardiac changes. *Wien Med Wochenschr*. 1994;144(16):399-406. PMID: 7856214

A variety of immunological and hormonal abnormalities were found in a group of CFS patients.

*

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Lieberman J, Bell DS. Serum angiotensin-converting enzyme as a marker for the chronic fatigue-immune dysfunction syndrome: a comparison to serum angiotensin-converting enzyme in sarcoidosis. *Am J Med.* 1993 Oct;95(4):407-12. PMID: 8213873

Serum ACE elevations may be a useful marker for CFIDS.

*

Demitrack MA, Gold PW, Dale JK, Krahn DD, Kling MA, Straus SE. Plasma and cerebrospinal fluid monoamine metabolism in patients with chronic fatigue syndrome: preliminary findings. *Biol Psychiatry.* 1992 Dec 15;32(12):1065-77. PMID: 1282370

A group of CFS patients showed a significant reduction in basal plasma levels of MHPG and a significant increase in basal plasma levels of 5-HIAA.

*

Kuratsune H, Yamaguti K, Hattori H, Tazawa H, Takahashi M, Yamanishi K, Kitani T. Symptoms, signs and laboratory findings in patients with chronic fatigue syndrome. *Nihon Rinsho.* 1992 Nov;50(11):2665-72. PMID: 1337562

The characteristic abnormality in CFS patients is the low values of 17-Ketosteroid-Sulfates/creatinine in morning urine and the acetylcarnitine deficiency.

Channelopathies

Fulle S, Belia S, Vecchiet J, Morabito C, Vecchiet L, Fanò G. Modification of the functional capacity of sarcoplasmic reticulum membranes in patients suffering from chronic fatigue syndrome. *Neuromuscul Disord.* 2003 Aug;13(6):479-84. PMID: 12899875

The sarcolemmal conduction system and some aspects of Ca²⁺ transport are negatively influenced in chronic fatigue syndrome. Both deregulation of pump activities (Na⁺/K⁺) and Ca²⁺-ATPase) and alteration in the opening status of ryanodine channels may result from increased membrane fluidity involving sarcoplasmic reticulum membranes.

*

Chaudhuri A, Watson WS, Pearn J, Behan PO. The symptoms of chronic fatigue syndrome are related to abnormal ion channel function. *Med Hypotheses.* 2000 Jan;54(1):59-63. PMID: 10790725

The authors hypothesize that abnormal ion channel function underlies the symptoms of CFS.

*

Waxman SG, Ptacek LJ. Chronic fatigue syndrome and channelopathies. *Med Hypotheses.* 2000 Nov;55(5):457. PMID: 11058431

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Lund-Olesen LH, Lund-Olesen K. The etiology and possible treatment of chronic fatigue syndrome/fibromyalgia. *Med Hypotheses*. 1994 Jul;43(1):55-8. PMID: 7968720

It is suggested that chronic fatigue syndrome/fibromyalgia is caused by virus injury to the calcium channels leading to larger quantities than usual of calcium ions entering the striated muscle cells.

Lipids

Maes M, Mihaylova I, Leunis JC. In chronic fatigue syndrome, the decreased levels of omega-3 poly-unsaturated fatty acids are related to lowered serum zinc and defects in T cell activation. *Neuro Endocrinol Lett*. 2005 Dec;26(6):745-51. PMID: 16380690

The results of this study show that a decreased availability of omega3 poly-unsaturated fatty acids plays a role in the pathophysiology of CFS and is related to the immune pathophysiology of CFS.

*

Liu Z, Wang D, Xue Q, Chen J, Li Y, Bai X, Chang L. Determination of fatty acid levels in erythrocyte membranes of patients with chronic fatigue syndrome. *Nutr Neurosci*. 2003 Dec;6(6):389-92.

Levels of the arachidonic acid (ARA) and docosahexanoic acid (DHA) were decreased in patients suffered from CFS. However, the levels of the palmitic acid and oleic acid were increased. We speculated that there are two possible mechanisms--one of which is that oxidative stress has led to an excessive oxidation and resulting in the above fatty acids. Alternatively, insufficiency of ingestion of fatty acids might not be the major cause.

*

Gray JB, Martinovic AM. Eicosanoids and essential fatty acid modulation in chronic disease and the chronic fatigue syndrome. *Med Hypotheses*. 1994 Jul;43(1):31-42. PMID: 7968718

The authors suggest that essential fatty acids may play a role in CFS.

*

Ogawa R, Toyama S, Matsumoto H. Chronic fatigue syndrome--cases in the Kanebo Memorial Hospital. *Nihon Rinsho*. 1992 Nov;50(11):2648-52. PMID: 1337561

Some CFS patients in this study had mild elevation of antibodies against Epstein-Barr Virus and immunologic abnormalities (natural killer cell dysfunction and high rates of skin reactivity to house dust, pollen, drugs and common food). In these patients, the researchers found decreases in serum concentrations of arachidonic acid and dihomogamma-linolenic acid.

*

Horrobin DF. Post-viral fatigue syndrome, viral infections in atopic eczema, and essential fatty acids. *Med Hypotheses*. 1990 Jul;32(3):211-7. PMID: 2204789

The authors propose an interaction between infections and essential fatty acid metabolism in post viral

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fatigue syndrome.

Carnitine

Reuter SE, Evans AM. Long-chain acylcarnitine deficiency in patients with chronic fatigue syndrome. Potential involvement of altered carnitine palmitoyltransferase-I activity. *J Intern Med.* 2010 Dec 22. PMID: 21205027

CFS patients demonstrate disturbance in carnitine homeostasis, possibly reflective of a reduction in carnitine palmitoyltransferase-I (CPT-I) activity.

*

Jones MG, Goodwin CS, Amjad S, Chalmers RA. Plasma and urinary carnitine and acylcarnitines in chronic fatigue syndrome. *Clin Chim Acta.* 2005 Oct;360(1-2):173-7. PMID: 15967423

CFS patients did not differ from controls in terms of plasma or urinary total, free or esterified (acyl) carnitine or in renal excretion rates of these compounds.

*

Kuratsune H, Yamaguti K, Lindh G, Evengard B, Takahashi M, Machii T, Matsumura K, Takaishi J, Kawata S, Långström B, Kanakura Y, Kitani T, Watanabe Y. Low levels of serum acylcarnitine in chronic fatigue syndrome and chronic hepatitis type C, but not seen in other diseases. *Int J Mol Med.* 1998 Jul;2(1):51-6. PMID: 9854142

A significant decrease in the levels of serum acetylcarnitine was found in patients with CFS.

*

Plioplys AV, Plioplys S. Serum levels of carnitine in chronic fatigue syndrome: clinical correlates. *Neuropsychobiology.* 1995;32(3):132-8. PMID: 8544970

CFS patients have statistically significantly lower serum total carnitine, free carnitine and acylcarnitine levels. Higher serum carnitine levels correlated with better functional capacity. These findings may be indicative of mitochondrial dysfunction.

*

Kuratsune H, Yamaguti K, Takahashi M, Misaki H, Tagawa S, Kitani T. Acylcarnitine deficiency in chronic fatigue syndrome. *Clin Infect Dis.* 1994 Jan;18 Suppl 1:S62-7. PMID: 8148455

A group of CFS patients had a deficiency of serum acylcarnitine.

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Nutrients

Mikirova N, Casciari J, Hunninghake R. The assessment of the energy metabolism in patients with chronic fatigue syndrome by serum fluorescence emission. *Altern Ther Health Med.* 2012 Jan-Feb;18(1):36-40. PMID: 22516851

The researchers determined that NADH levels could be used to gauge health status of CFS patients.

*

Blankfield A. A Brief Historic Overview of Clinical Disorders Associated with Tryptophan: The Relevance to Chronic Fatigue Syndrome (CFS) and Fibromyalgia (FM). *Int J Tryptophan Res.* 2012;5:27-32. PMID: 23032646

The current paper will focus on the emerging role of tryptophan deficiencies in CFS and fibromyalgia.

*

Antiel RM, Caudill JS, Burkhardt BE, Brands CK, Fischer PR. Iron insufficiency and hypovitaminosis D in adolescents with chronic fatigue and orthostatic intolerance. *South Med J.* 2011 Aug;104(8):609-11. PMID: 21886073

In patients presenting with chronic fatigue and/or orthostatic intolerance, low ferritin levels and hypovitaminosis D are common, especially in patients with excessive postural tachycardia.

*

Berkovitz S, Ambler G, Jenkins M, Thurgood S. Serum 25-hydroxy vitamin D levels in chronic fatigue syndrome: a retrospective survey. *Int J Vitam Nutr Res.* 2009 Jul;79(4):250-4. PMID: 20209476

25-OH vitamin D levels are moderately to severely suboptimal in CFS patients, with a mean of 44.4 nmol/L (optimal levels >75 nmol/L). These levels are lower and the

difference is statistically significant ($p < 0.0004$) than those of the general British population from a recent national survey, but similar to those in patients with other chronic conditions.

*

McCully KK, Malucelli E, Iotti S. Increase of free Mg²⁺ in the skeletal muscle of chronic fatigue syndrome patients. *Dyn Med.* 2006 Jan 11;5:1. PMID: 16405724

CFS patients had higher resting free Mg²⁺ levels compared to sedentary controls.

*

Heap LC, Peters TJ, Wessely S. Vitamin B status in patients with chronic fatigue syndrome. *J R Soc Med.* 1999 Apr;92(4):183-5. PMID: 10450194

There is a reduced functional B vitamin status, particularly of pyridoxine, in CFS patients.

*

Jacobson W, Saich T, Borysiewicz LK, Behan WM, Behan PO, Wreghitt TG. Serum folate and chronic fatigue

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syndrome. *Neurology*. 1993 Dec;43(12):2645-7. PMID: 8255470

Half of a group of CFS patients were deficient in folic acid.

CFS vs. Other Conditions

Morris G, Anderson G, Galecki P, Berk M, Maes M. A narrative review on the similarities and dissimilarities between myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and sickness behavior. *BMC Med*. 2013 Mar 8;11(1):64. PMID: 23497361

Differences and similarities between sickness behavior (an adaptive response induced by proinflammatory cytokines) and ME/CFS are discussed. The article concludes that these are two different conditions.

*

Abbi B, Natelson BH. Is chronic fatigue syndrome the same illness as fibromyalgia: evaluating the 'single syndrome' hypothesis. *QJM*. 2013 Jan;106(1):3-9. PMID: 22927538

This review presents data showing differences between CFS and FM across a number of parameters.

*

Katz BZ, Stewart JM, Shiraishi Y, Mears CJ, Taylor R. Orthostatic tolerance testing in a prospective cohort of adolescents with chronic fatigue syndrome and recovered controls following infectious mononucleosis. *Clin Pediatr (Phila)*. 2012 Sep;51(9):835-9. PMID:22850676

This study suggests that adolescents who meet criteria for CFS 6 months following infectious mononucleosis do not have, as a group, more standing orthostatic intolerance than recovered controls.

*

Itoh Y, Shigemori T, Igarashi T, Fukunaga Y. Fibromyalgia And Chronic Fatigue Syndrome In Children. *Pediatr Int*. 2011 Nov 24. PMID: 22115414

In a group of children, ANA titers were higher and the prevalence of anti-Sa was far more frequent in CFS patients than in FM cases. The authors conclude that CFS and FM are different from each other at least in childhood from the immunological aspects, although a few patients were suffering from both conditions.

*

Ciccone DS, Weissman L, Natelson BH. Chronic fatigue syndrome in male Gulf war veterans and civilians: a further test of the single syndrome hypothesis. *J Health Psychol*. 2008 May;13(4):529-36. PMID: 18420761

CFS was more likely to present in a sudden flu-like manner in civilians than Gulf War veterans. Comorbid fibromyalgia was more prevalent in civilians.

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Sinaii N, Cleary SD, Ballweg ML, Nieman LK, Stratton P. High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis. *Hum Reprod.* 2002 Oct;17(10):2715-24. PMID: 12351553

A survey showed that about 4.6% of endometriosis sufferers also reported having CFS.

*

Aaron LA, Herrell R, Ashton S, Belcourt M, Schmaling K, Goldberg J, Buchwald D. Comorbid clinical conditions in chronic fatigue: a co-twin control study. *J Gen Intern Med.* 2001 Jan;16(1):24-31. PMID: 11251747

Compared to their nonfatigued co-twins, CFS twins had higher rates of fibromyalgia and irritable bowel syndrome. The strongest associations were observed between chronic

fatigue and fibromyalgia, irritable bowel syndrome, chronic pelvic pain, multiple chemical sensitivities, and temporomandibular disorder.

*

White KP, Speechley M, Harth M, Ostbye T. Co-existence of chronic fatigue syndrome with fibromyalgia syndrome in the general population. A controlled study. *Scand J Rheumatol.* 2000;29(1):44-51. PMID: 10722257

There is significant clinical overlap between CFS and FMS.

*

Evengard B, Nilsson CG, Lindh G, Lindquist L, Eneroth P, Fredrikson S, Terenius L, Henriksson KG. Chronic fatigue syndrome differs from fibromyalgia. No evidence for elevated substance P levels in cerebrospinal fluid of patients with chronic fatigue syndrome. *Pain.* 1998 Nov;78(2):153-5. PMID: 9839828

Unlike fibromyalgia patients, CFS patients have normal levels of Substance P in their cerebrospinal fluid.

*

De Lorenzo F, Hargreaves J, Kakkar VV. Phosphate diabetes in patients with chronic fatigue syndrome. *Postgrad Med J.* 1998 Apr;74(870):229-32. PMID: 9683977

The authors report a relationship between chronic fatigue syndrome and phosphate diabetes.

HLA

Spitzer AR, Broadman M. A retrospective review of the sleep characteristics in patients with chronic fatigue syndrome and fibromyalgia. *Pain Pract.* 2010 Jul-Aug;10(4):294-300. PMID: 20230458

HLA DQB1*0602 was obtained in 74 patients, and positive in 32 (43%), $P < 0.0001$. In patients with CFS and fibromyalgia, researchers found a sleep disorder characterized by objective hypersomnia. Seventy-three

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(80%) were on an abnormal multiple sleep latency testing (MSLT). Some patients had characteristics of narcolepsy. Highly fragmented sleep was seen.

*

Carlo-Stella N, Bozzini S, De Silvestri A, Sbarsi I, Pizzochero C, Lorusso L, Martinetti M, Cuccia M. Molecular study of receptor for advanced glycation endproduct gene promoter and identification of specific HLA haplotypes possibly involved in chronic fatigue syndrome. *Int J Immunopathol Pharmacol.* 2009 Jul-Sep;22(3):745-54. PMID: 19822091

Certain HLA DRB genetic types (related to the acquired immune system) are more associated with CFS than are others.

*

Ortega-Hernandez OD, Cuccia M, Bozzini S, Bassi N, Moscovitch S, Diaz-Gallo LM, Blank M, Agmon-Levin N, Shoenfeld Y. Autoantibodies, polymorphisms in the serotonin pathway, and human leukocyte antigen class II alleles in chronic fatigue syndrome: are they associated with age at onset and specific symptoms? *Ann N Y Acad Sci.* 2009 Sep;1173:589-99. PMID: 19758204

HLA DRB genetic types are related to symptom presentation and age of onset in CFS.

*

Smith J, Fritz EL, Kerr JR, Cleare AJ, Wessely S, Matthey DL. Association of chronic fatigue syndrome with human leukocyte antigen class II alleles. *J Clin Pathol.* 2005 Aug;58(8):860-3. PMID: 16049290

Forty nine patients with CFS were genotyped for the HLA-DRB1, HLA-DQA1, and HLA-DQB1 alleles and the frequency of these alleles was compared with a control group comprising 102 normal individuals from the UK. Analysis by 2 x 2 contingency tables revealed an increased frequency of HLA-DQA1*01 alleles in patients with CFS (51.0% v 35%; odds ratio (OR), 1.93; p = 0.008). HLA-DQB1*06 was also increased in the patients with CFS (30.2% v 20.0%; OR, 1.73, p = 0.052). Only the association between HLA-DQA1*01 and CFS was significant in logistic regression models containing HLA-DQA1*01 and HLA-DRQB1*06, and this was independent of HLA-DRB1 alleles. There was a decreased expression of HLA-DRB1*11 in CFS, although this association disappeared after correction for multiple comparisons. CFS may be associated with HLA-DQA1*01, although a role for other genes in linkage disequilibrium cannot be ruled out.

*

Underhill JA, Mahalingam M, Peakman M, Wessely S. Lack of association between HLA genotype and chronic fatigue syndrome. *Eur J Immunogenet.* 2001 Jun;28(3):425-8. PMID:11422420

Fifty-eight patients were phenotyped for HLA A and B by microcytotoxicity and genotyped for HLA DRB, DQB and DPB by PCR oligoprobing, and the frequencies of antigens so

assigned were compared with those from a control group of 134. No significant differences in HLA frequencies were found between patient and control groups.

*

Itoh Y, Igarashi T, Tatsuma N, Imai T, Yoshida J, Tsuchiya M, Murakami M, Fukunaga Y. Immunogenetic background of patients with autoimmune fatigue syndrome. *Autoimmunity.* 2000 Oct;32(3):193-7.

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PMID: 11092699

We hypothesized that if autoimmune mechanisms did play an important role in the pathogenesis of AIFS, it is possible that it is immunogenetically regulated as observed in other autoimmune disorders. In order to examine the immunogenetic background of AIFS patients, HLA-A, -B, -C, and -DR loci were analyzed serologically in 61 AIFS patients. AIFS was found to be positively associated with the class I antigen HLA-B61 and with the class II antigen HLA-DR9, with odds ratios of 2.77 ($p = 0.015$, $P_{corr} = 0.48$) and 2.60 ($p = 0.012$, $P_{corr} = 0.17$), respectively. A negative association was also found between AIFS and HLA-DR2 with odds ratio of 0.25 ($p = 0.029$, $P_{corr} = 0.041$). When comparing anti-Sa positive AIFS patients with healthy controls, the odds ratios associated with HLA-B61, DR9, and DR2 were 3.42 ($p = 0.021$, $P_{corr} = 0.22$), 3.96 ($p = 0.0011$, $P_{corr} = 0.015$), and 0.16 ($p = 0.0022$, $P_{corr} = 0.031$), respectively. Thus, the HLA associations observed in this study suggested that immunogenetic background might play a role in AIFS.

*

Hassan IS, Bannister BA, Akbar A, Weir W, Bofill M. A study of the immunology of the chronic fatigue syndrome: correlation of immunologic parameters to health dysfunction. *Clin Immunol Immunopathol.* 1998 Apr;87(1):60-7. PMID: 9576011

CFS patients had significantly increased mean fluorescence intensity readings of HLA-DR in CD4 and CD8 cells ($P < 0.05$). Expression of the costimulatory receptor CD28 in CD8 cells was significantly reduced, and the apoptosis repressor ratio of bcl-2/bax in both CD4 and CD8 was increased in patients ($P < 0.05$). Patients with increased HLA-DR expression had significantly lower SF-36 total scores, worse body pains, and poorer general health perception and physical functioning scores. Increased spontaneous lymphocyte proliferation was associated with poor general health perception.

*

Keller RH, Lane JL, Klimas N, Reiter WM, Fletcher MA, van Riel F, Morgan R. Association between HLA class II antigens and the chronic fatigue immune dysfunction syndrome. *Clin Infect Dis.* 1994 Jan;18 Suppl 1:S154-6. PMID: 8148444

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Middleton D, Savage DA, Smith DG. No association of HLA class II antigens in chronic fatigue syndrome. *Dis Markers.* 1991 Jan-Feb;9(1):47-9. PMID: 1683826

*

van Greure CH, Bouic PJ. Aberrant in vitro HLA-DR expression in patients with chronic fatigue. *S Afr Med J.* 1990 Aug 18;78(4):219-20. PMID: 2382182

Gene Expression

Cifuentes RA, Barreto E. Supervised selection of single nucleotide polymorphisms in chronic fatigue syndrome. *Biomedica.* 2011 Oct-Dec;31(4):613-21. PMID: 22674373

The researchers created a valid profile of polymorphisms for CFS, including two known polymorphisms

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associated with chronic fatigue syndrome, the NR3C1_11159943 major allele and the 5HTT_7911132 minor allele.

*

Light KC, White AT, Tadler S, Iacob E, Light AR. Genetics and Gene Expression Involving Stress and Distress Pathways in Fibromyalgia with and without Comorbid Chronic Fatigue Syndrome. *Pain Res Treat.* 2012;2012:427869. PMID: 22110941

This paper summarizes research on genes that may be linked to increased susceptibility in developing and maintaining CFS and fibromyalgia, and research on resting and stressor-evoked changes in leukocyte gene expression, highlighting physiological pathways linked to stress and distress. These include the adrenergic nervous system, the hypothalamic-pituitary-adrenal axis and serotonergic pathways, and exercise responsive metabolite-detecting ion channels. The findings to date provide some support for both inherited susceptibility and/or physiological dysregulation in all three systems, particularly for catechol-O-methyl transferase (COMT) genes, the glucocorticoid and the related mineralocorticoid receptors (NR3C1, NR3C2), and the purinergic 2X4 (P2X4) ion channel involved as a sensory receptor for muscle pain and fatigue and also in upregulation of spinal microglia in chronic pain models.

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Sommerfeldt L, Portilla H, Jacobsen L, Gjerstad J, Wyller VB. Polymorphisms of adrenergic cardiovascular control genes are associated with adolescent chronic fatigue syndrome. *Acta Paediatr.* 2011 Feb;100(2):293-8. PMID: 21059181

CFS patients were especially likely to have a number of specific genes, suggesting that CFS might be related to polymorphisms of COMT and the β_2 -adrenergic receptor.

Smith AK, Fang H, Whistler T, Unger ER, Rajeevan MS. Convergent Genomic Studies Identify Association of GRIK2 and NPAS2 with Chronic Fatigue Syndrome. *Neuropsychobiology.* 2011;64(4):183-94. PMID: 21912186

Using an integrated genomic strategy, this study suggests a possible role for genes involved in glutamatergic neurotransmission and circadian rhythm in CFS and supports further study of novel candidate genes in independent populations of CFS subjects.

*

Falkenberg VR, Whistler T, Murray JR, Unger ER, Rajeevan MS. Identification of Phosphoglycerate Kinase 1 (PGK1) as a Reference Gene for Quantitative Gene Expression Measurements in Human Blood RNA. *BMC Res Notes.* 2011 Sep 6;4(1):324. PMID: 21896205

Reference genes that may be suitable for the analysis of CFS, or human blood RNA derived from whole blood as well as isolated peripheral blood mononuclear cells (PBMCs), have not previously been described. The authors identified PGK1 as a stable reference gene for use with whole blood RNA and RNA.

*

Sommerfeldt L, Portilla H, Jacobsen L, Gjerstad J, Wyller VB. Polymorphisms of adrenergic cardiovascular control genes are associated with adolescent chronic fatigue syndrome. *Acta Paediatr.* 2011 Feb;100(2):293-8. PMID: 21059181

CFS patients were especially likely to have a number of specific genes, suggesting that CFS

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might be related to polymorphisms of COMT and the β_2 -adrenergic receptor.

*

Falkenberg VR, Gurbaxani BM, Unger ER, Rajeevan MS. Functional Genomics of Serotonin Receptor 2A (HTR2A): Interaction of Polymorphism, Methylation, Expression and Disease Association. *Neuromolecular Med.* 2011 Mar;13(1):66-76. PMID: 20941551

This study of CFS patients suggests that the promoter polymorphism (rs6311) can affect both transcription factor binding and promoter methylation, and this along with an individual's stress response can impact the rate of HTR2A transcription in a genotype and methylation-dependent manner.

*

Fukuda S, Hashimoto R, Ohi K, Yamaguti K, Nakatomi Y, Yasuda Y, Kamino K, Takeda M, Tajima S, Kuratsune H, Nishizawa Y, Watanabe Y. A functional polymorphism in the disrupted-in schizophrenia 1 gene is associated with chronic fatigue syndrome. *Life Sci.* 2010 May 8;86(19-20):722-5. PMID: 20227423

The Cys704 allele of Ser704Cys SNP was associated with an increased risk of CFS development compared with the Ser704 allele.

*

Landmark-Høyvik H, Reinertsen KV, Loge JH, Kristensen VN, Dumeaux V, Fosså SD, Børresen-Dale AL, Edvardsen H. The genetics and epigenetics of fatigue. *PM R.* 2010 May;2(5):456-65. PMID: 20656628

A systems biology approach that includes environmental influences needs to be taken in order to look at the role of genetics in CFS.

*

Zhang L, Gough J, Christmas D, Matthey DL, Richards SC, Main J, Enlander D, Honeybourne D, Ayres JG, Nutt DJ, Kerr JR. Microbial infections in eight genomic subtypes of chronic fatigue syndrome/myalgic encephalomyelitis. *J Clin Pathol.* 2010 Feb;63(2):156-64. PMID: 19955554

Specific genotypes are associated with CFS.

*

Huang LC, Hsu SY, Lin E. A comparison of classification methods for predicting Chronic Fatigue Syndrome based on genetic data. *J Transl Med.* 2009 Sep 22;7:81. PMID:19772600

The authors compared computational tools with and without feature selection for predicting chronic fatigue syndrome (CFS) using genetic factors such as single nucleotide polymorphisms (SNPs).

*

Gow JW, Hagan S, Herzyk P, Cannon C, Behan PO, Chaudhuri A. A gene signature for post-infectious chronic fatigue syndrome. *BMC Med Genomics.* 2009 Jun 25;2:38. PMID: 19555476

Differentially expressed genes in CFS suggest problems with immune modulation, oxidative stress and apoptosis. These may have the potential of serving as biomarkers for the disease.

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Byrnes A, Jacks A, Dahlman-Wright K, Evengard B, Wright FA, Pedersen NL, Sullivan PF. Gene expression in peripheral blood leukocytes in monozygotic twins discordant for chronic fatigue: no evidence of a biomarker. *PLoS One*. 2009 Jun 5;4(6):e5805. PMID: 19503787

The authors were unable to identify a biomarker for chronic fatiguing illness in the transcriptome of peripheral blood leukocytes.

*

Lin E, Hsu SY. A Bayesian approach to gene-gene and gene-environment interactions in chronic fatigue syndrome. *Pharmacogenomics*. 2009 Jan;10(1):35-42. PMID: 19102713

The Bayesian based approach is a promising method to assess the gene-gene and gene-environment interactions in chronic fatigue syndrome patients by using genetic factors, such as SNPs, and demographic factors such as age, gender and BMI.

*

Saiki T, Kawai T, Morita K, Ohta M, Saito T, Rokutan K, Ban N. Identification of marker genes for differential diagnosis of chronic fatigue syndrome. *Mol Med*. 2008 Sep-Oct;14(9-10):599-607. PMID: 18596870

A defined gene cluster (9 genes) may be useful for detecting pathological responses in CFS patients and for differential diagnosis of this syndrome.

*

Kerr JR. Gene profiling of patients with chronic fatigue syndrome/myalgic encephalomyelitis. *Curr Rheumatol Rep*. 2008 Dec;10(6):482-91. PMID: 19007540

A total of 88 human genes were upregulated or downregulated in CFS patients, including those related to hematologic function, immunologic function, cancer, cell death, immune response and infection.

*

Presson AP, Sobel EM, Papp JC, Suarez CJ, Whistler T, Rajeevan MS, Vernon SD, Horvath S. Integrated weighted gene co-expression network analysis with an application to chronic fatigue syndrome. *BMC Syst Biol*. 2008 Nov 6;2:95. PMID: 18986552

A systems biology approach was used to create a module of 299 highly correlated genes associated with CFS severity.

*

Kerr JR, Petty R, Burke B, Gough J, Fear D, Sinclair LI, Matthey DL, Richards SC, Montgomery J, Baldwin DA, Kellam P, Harrison TJ, Griffin GE, Main J, Enlander D, Nutt DJ, Holgate ST. Gene expression subtypes in patients with chronic fatigue syndrome/myalgic encephalomyelitis. *J Infect Dis*. 2008 Apr 15;197(8):1171-84. PMID: 18462164

The researchers analyzed gene expression in peripheral blood from 25 patients with CFS.

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Kerr JR, Burke B, Petty R, Gough J, Fear D, Matthey DL, Axford JS, Dalgleish AG, Nutt DJ. Seven genomic subtypes of chronic fatigue syndrome/myalgic encephalomyelitis: a detailed analysis of gene networks and clinical phenotypes. *J Clin Pathol*. 2008 Jun;61(6):730-9. PMID: 18057078

Clustering of quantitative PCR (qPCR) data from patients with CFS revealed seven distinct subtypes.

*

Smith AK, Dimulescu I, Falkenberg VR, Narasimhan S, Heim C, Vernon SD, Rajeevan MS. Genetic evaluation of the serotonergic system in chronic fatigue syndrome. *Psychoneuroendocrinology*. 2008 Feb;33(2):188-97. PMID: 18079067

Sequence variation in HTR2A, related to serotonin, may potentially result in its enhanced activity and thus be involved in the pathophysiology of CFS.

*

Kawai T, Rokutan K. Identification and application of marker genes for differential diagnosis of chronic fatigue syndrome. *Nihon Rinsho*. 2007 Jun;65(6):1029-33. PMID: 17561693

The authors identified 9 genes that were significantly and differentially expressed between CFS patients and healthy subjects.

*

Narita M, Narita N. Genetic background of chronic fatigue syndrome. *Nihon Rinsho*. 2007 Jun;65(6):997-1002. PMID: 17561688

A significant increase of longer (L and XL) allelic variants for serotonin transporter was found in the CFS patients compared to the controls. Compared to S allele, the L allele is believed to retain higher transcriptional activity, which causes decreased concentration of serotonin in the extracellular space, namely, active serotonin in CFS.

*

Rajeevan MS, Smith AK, Dimulescu I, Unger ER, Vernon SD, Heim C, Reeves WC. Glucocorticoid receptor polymorphisms and haplotypes associated with chronic fatigue syndrome. *Genes Brain Behav*. 2007 Mar;6(2):167-76. PMID: 16740143

The authors observed an association of multiple SNPs with chronic fatigue compared to non-fatigued (NF) subjects.

*

Fang H, Xie Q, Boneva R, Fostel J, Perkins R, Tong W. Gene expression profile exploration of a large dataset on chronic fatigue syndrome. *Pharmacogenomics*. 2006 Apr;7(3):429-40. PMID: 16610953

In a population of CFS sufferers, researchers identified 24 common genes and 11 common pathways.

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Whistler T, Taylor R, Craddock RC, Broderick G, Klimas N, Unger ER. Gene expression correlates of unexplained fatigue. *Pharmacogenomics*. 2006 Apr;7(3):395-405. PMID: 16610950

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A total of 839 genes were statistically associated with fatigue measures. These mapped to biological pathways such as oxidative phosphorylation, gluconeogenesis, lipid metabolism, and several signal transduction pathways. The study supports the use of phenotypic measures of CFS and QTA as important for additional studies of this complex illness.

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Vernon SD, Whistler T, Aslakson E, Rajeevan M, Reeves WC. Challenges for molecular profiling of chronic fatigue syndrome. *Pharmacogenomics*. 2006 Mar;7(2):211-8. PMID: 16515400

The peripheral blood appears to be facilitating the molecular profiling of several diseases, such as CFS, that involve bodywide perturbations that are mediated by the CNS.

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Goertzel BN, Pennachin C, de Souza Coelho L, Gurbaxani B, Maloney EM, Jones JF. Combinations of single nucleotide polymorphisms in neuroendocrine effector and receptor genes predict chronic fatigue syndrome. *Pharmacogenomics*. 2006 Apr;7(3):475-83. PMID: 16610957

The authors suggest that the fact that only 28 out of several million possible SNPs predict whether a person has CFS with 76% accuracy indicates that CFS has a genetic component that may help to explain some aspects of the illness.

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Kaushik N, Fear D, Richards SC, McDermott CR, Nuwaysir EF, Kellam P, Harrison TJ, Wilkinson RJ, Tyrrell DA, Holgate ST, Kerr JR. Gene expression in peripheral blood mononuclear cells from patients with chronic fatigue syndrome. *J Clin Pathol*. 2005 Aug;58(8):826-32. PMID: 16049284

CFS patients showed gene upregulations typical of T cell activation and perturbation of neuronal and mitochondrial function.

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Vernon SD, Reeves WC. Evaluation of autoantibodies to common and neuronal cell antigens in Chronic Fatigue Syndrome. *J Autoimmune Dis*. 2005 May 25;2:5. PMID: 15916704

Subsets of those with CFS had higher rates of antibodies to microtubule-associated protein 2 (MAP2) and ssDNA. There was no evidence of higher rates for several common nuclear and cellular antigens in people with CFS.

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Torpy DJ, Bachmann AW, Gartside M, Grice JE, Harris JM, Clifton P, Easteal S, Jackson RV, Whitworth JA. Association between chronic fatigue syndrome and the corticosteroid-binding globulin gene ALA SER224 polymorphism. *Endocr Res*. 2004 Aug;30(3):417-29. PMID: 15554358

Homozygosity for the serine allele of the CBG gene may predispose to CFS, perhaps due to an effect on hypothalamic-pituitary-adrenal axis function related to altered CBG-cortisol transport function or immune-cortisol interactions.

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Whistler T, Unger ER, Nisenbaum R, Vernon SD. Integration of gene expression, clinical, and epidemiologic data to characterize Chronic Fatigue Syndrome. *J Transl Med.* 2003 Dec 1;1(1):10. PMID: 14641939

Differentially expressed genes in CFS were involved in pathways of purine and pyrimidine metabolism, glycolysis, oxidative phosphorylation, and glucose metabolism.

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Powell R, Ren J, Lewith G, Barclay W, Holgate S, Almond J. Identification of novel expressed sequences, up-regulated in the leucocytes of chronic fatigue syndrome patients. *Clin Exp Allergy.* 2003 Oct;33(10):1450-6. PMID: 14519154

The identification of novel gene tags up-regulated in CFS patients suggests that CFS is a disease characterized by subtle changes in the immune system.

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Vernon SD, Unger ER, Dimulescu IM, Rajeevan M, Reeves WC. Utility of the blood for gene expression profiling and biomarker discovery in chronic fatigue syndrome. *Dis Markers.* 2002;18(4):193-9. PMID: 12590173

Several of the differentially expressed genes are associated with immunologic functions (e.g., CMRF35 antigen, IL-8, HD protein) and implicate immune dysfunction in the pathophysiology of CFS.

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Vernon SD, Shukla SK, Conradt J, Unger ER, Reeves WC. Analysis of 16S rRNA gene sequences and circulating cell-free DNA from plasma of chronic fatigue syndrome and non-fatigued subjects. *BMC Microbiol.* 2002 Dec 23;2:39. PMID:12498618

CFS subjects had slightly lower concentrations or no detectable plasma DNA than non-fatigued subjects. There was a diverse array of 16S rDNA sequences in plasma DNA from both CFS and non-fatigued subjects. There were no unique, previously uncharacterized or predominant 16S rDNA sequences in either CFS or non-fatigued subjects.

Updated 05.06.14

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ⁱ Dr. Susan Maier's presentation to the IOM Panel for Diagnostic Criteria on January 27-28, 2014

<http://www.iom.edu/~media/Files/Activity%20Files/Disease/MECFS/Maier%20IOM%20MECFS%20Presentation.pdf>

a. How do ME and CFS differ?

- i. Do these illnesses lie along the same continuum of severity or are they entirely separate symptoms?
- ii. What makes them different, what makes them the same?
- iii. What is lacking in each case definition – do the non-overlapping elements of each case definition identify a subset of the illness or do they encompass the entirety of the population?

ⁱⁱ According to a discussion at the June 2014 CFSAC, these questions were apparently removed from the P2P evidence review protocol because there is "not enough evidence" in the literature to consider this question.

<http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac-minutes-june-17-2014.pdf> page 38

ⁱⁱⁱ Jason has a substantial body of evidence on this issue. Two of the articles include

- Jason, L., Richman, J., Friedberg, F., Wagner, L., Taylor, R., Jordan, K. Politics science and the emergence of a new disease. September 1997, *American Psychologist*. Vol. 52, No. 9, 973-983 (Exclusion code: not given)

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 - ^{iv} Jason, L., Najjar, N., Porter, N., Reh, C. Evaluating the Centers for Disease Control’s Empirical Chronic Fatigue Syndrome Case Definition. *Journal of Disability Policy Studies* Oct 2008,
 - ^v Jason LA, Evans M, Brown A, et al. Sensitivity and specificity of the CDC empirical chronic fatigue syndrome case definition. *Psychology*. 2010;1(1): 9-16. PMID: 23685416.
 - ^{vi} Publications for the Wichita Surveillance study include
 - Reyes M, Nisenbaum R, Hoaglin DC, Unger ER, Emmons C, Randall B, Stewart JA, Abbey S, Jones JF, Gantz N, Minden S, Reeves WC: Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas. *Arch Intern Med*. 2003 Jul 14;163(13):1530-6. (Exclusion code: not given)
 - Solomon L, Nisenbaum R, Reyes M, Papanicolaou DA, Unger ER, Reeves WC: Functional status of persons with chronic fatigue syndrome in the Wichita population. *BMC Hlth Quality Life Outcomes* 2003, 1:48. (Exclusion code: not given)
 - Nisenbaum R, Jones JF, Unger ER, Reyes M, Reeves WC: A population based study of the clinical course of chronic fatigue syndrome. *BMC Hlth Quality Life Outcomes* 2003, 1:49. (Exclusion code: 2) “ About one-third of CFS subjects retained the classification after 1 year of follow-up (Table 6). At 2 and 3 years follow-up, only 21% of the subjects were classified as having CFS. Most transitioned into a non-CFS state because of insufficient symptoms or fatigue severity, absence of fatigue, or identification of an exclusionary condition. Overall, 23.1% (15 of 65) were eventually diagnosed with permanent exclusions.”
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 - ^x Reeves et al. "Chronic Fatigue Syndrome – A Clinically Empirical Approach to Its Definition and Study" in *BMC Medicine*. 2005, December 15. “most studies of CFS merely note that they used the 1994 case definition and they do not generally specify how disability, fatigue and symptom occurrence were elucidated. Thus, it is difficult to assess the validity of their diagnostic criteria and essentially impossible to compare results between studies critically.”
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- *The PACE trial, done in patients that met the Oxford definition, tested cognitive behavioral therapy (CBT) and graded exercise therapy (GET) which were used “on the basis of the fear avoidance theory of chronic fatigue syndrome” that “assume that the syndrome is perpetuated by reversible physiological changes of deconditioning and avoidance of activity.”*
 - *PACE trial CBT Manual - <http://www.pacetrial.org/docs/cbt-therapist-manual.pdf> Page 81 - “It is important to include the precipitating factors, e.g., illness, life-events, working excessively hard, perfectionist personality etc. It is also important to discuss the maintaining factors, e.g., erratic or reduced activities, disturbed sleep patterns, unhelpful illness beliefs and any other unhelpful cognitions etc.*
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- ^{xciii} The following two articles discuss this theory. The work of Wessely is referred to as the biopsychosocial approach where the work of Vercoulen was described by Maes as a psychosocial approach.
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- ^{xciv} Examples include the following:
- Certain English institutions and government agencies have incorrectly stated that the term “CFS” is classified not only as a neurological disorder but also as neurasthenia. In the 2001 British *WHO Guide to Mental Health in Primary Care*, adapted from the WHO’s guide to mental health in primary care, England placed CFS not only in

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the neurological chapter but also under neurasthenia in the mental and behavioral disorders chapter. In 2001 and again in 2004, WHO staff issued a ruling that the placement under neurasthenia was incorrect.

- Summary of statement by World Health Organization about the dual classification http://www.theoneclickgroup.co.uk/documents/ME-CFS_docs/WHO%20STATEMENT.doc
“Andre L’Hours, the Technical Officer at the WHO headquarters in Geneva who is responsible for the ICD, confirmed that it was “unacceptable” if the same disorder had been included in two places in the ICD-10 and that the same disorder could not be differently categorised under the one WHO banner.”
- WHO Guide to Mental Health In Primary Care” published by the WHO collaborating Center at Kings College. It is not clear exactly when this was first published but it is on the 2001 version of this page. <http://web.archive.org/web/20010709061548/http://cebmh.warne.ox.ac.uk/cebmh/whoguidemhpcuk/disorders/f48-0.html>
- The *Read Codes*, used as standard terminology in clinical practice in England, classifies CFS (and ME which is listed as a synonym of CFS) as both a neurological disorder and as a form of neurasthenia listed under somatoform disorders in the mental health disorders section.^{xciiv}
 - Read Codes <http://systems.hscic.gov.uk/data/uktc/readcodes>
 - Read Codes, Clinical Terms Version 3 (CTV3) can be seen here <http://bioportal.bioontology.org/ontologies/RCD?p=classes&conceptid=http%3A%2F%2Fpurl.bioontology.org%2Fontology%2FRCD%2FXa01F>
- The *SNOMED CT* clinical terminology system, important to the implementation of electronic health records, lists CFS as a multisystem disorder but also as a mental disorder. ME is listed as a synonym of CFS and thus similarly classified
 - <http://www.ihtsdo.org/snomed-ct/>
 - Multiple browsers are available, including: <http://bioportal.bioontology.org/ontologies/SNOMEDCT?p=classes&conceptid=http%3A%2F%2Fpurl.bioontology.org%2Fontology%2FSNOMEDCT%2F52702003>
- Training Module for Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME) - Guidelines for the Disability Analyst. Continuing Medical Education Programme Provided On Behalf Of The Department For Work And Pensions. MED/S2/CMEP~0017 Version 7 Final Module: 6. May 28, 2014. <http://www.actionforme.org.uk/Resources/Action%20for%20ME/dwp-training-doc-for-assessors-on-me.pdf>
 - In 2014, the U.K. Department of Work and Pensions issued a training module for “CFS/ME” disability assessment,^{xciiv} which also incorrectly states that the ICD-10 classifies the disease as both neurasthenia and a neurological disorder. But the manual goes further and explicitly links CFS/ME to the term “somatic symptom disorder” in the new version of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. The manual states that somatic symptom disorder is a newer term for somatoform disorder.
- Treatments for Fibromyalgia in Adult Subgroups. Agency for Healthcare Research and Quality. Draft July 23, 2014. Page 30 of file, page 4 of second section <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayProduct&productID=1944>The July 23, 2014 draft evidence review for
 - *Treatment for Fibromyalgia in Adult Subgroups*,^{xciiv} published by AHRQ, referred to CFS as a “functional somatic syndrome”, a term widely equated to the terms “somatoform illness” and “somatic symptom disorder.”

^{xcv} Examples of CFS being referred to as Somatorm illness.

- Overview - [Slide presentation](#) [PDF format] **Somatoform disorders – functional somatic syndromes – Bodily distress syndrome**. Need for care and organisation of care in an international perspective – EACLPP Lecture, Prof. Per Fink, MD, Ph.D, Dr.Med.Sc. www.functionaldisorders.dk
- Michael B. First, M.D., DSM Somatic Presentations of Mental Disorders (September 6-8, 2006). American Psychiatric Association. <http://www.dsm5.org/Research/Pages/SomaticPresentationsofMentalDisorders%28September6-8,2006%29.aspx>

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